EXHIBIT A70

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

VOLUME 100

A Review of Human Carcinogens

Part C: Arsenic, Metals, Fibres, and Dusts

LYON, FRANCE

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Volume 100

A Review of Human Carcinogens

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This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon,

17–24 March 2009

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields; and to indicate where additional research efforts are needed. The lists of IARC evaluations are regularly updated and are available on the Internet at http://monographs.iarc.fr/.

This programme has been supported since 1982 by Cooperative Agreement U01 CA33193 with the United States National Cancer Institute, Department of Health and Human Services. Additional support has been provided since 1986 by the Health, Safety and Hygiene at Work Unit of the European Commission Directorate-General for Employment, Social Affairs and Equal Opportunities, and since 1992 by the United States National Institute of Environmental Health Sciences, Department of Health and Human Services. The contents of this volume are solely the responsibility of the Working Group and do not necessarily represent the official views of the U.S. National Cancer Institute, the U.S. National Institute of Environmental Health Sciences, the U.S. Department of Health and Human Services, or the European Commission Directorate-General for Employment, Social Affairs and Equal Opportunities.

This volume was made possible, in part, through Cooperative Agreement CR 834012 with the United States Environmental Protection Agency, Office of Research and Development. The contents of this volume do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

Published by the International Agency for Research on Cancer,
150 cours Albert Thomas, 69372 Lyon Cedex 08, France

Distributed by WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland
(tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int).

IARC Library Cataloguing in Publication Data

A review of human carcinogens. Part C: arsenic, metals, fibres, and dusts/ IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2009: Lyon, France)

(IARC monographs on the evaluation of carcinogenic risks to humans ; v. 100C)

1. Arsenic – adverse effects 2. Carcinogens 3. Dust – adverse effects
4. Metals – adverse effects 5. Mineral Fibres – adverse effects 4. Neoplasms – etiology
I. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans
II. Series

ISBN 978 92 832 1320 8 (NLM Classification: W1)
ISSN 1017-1606

PRINTED IN FRANCE

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NOTE TO THE READER

The term 'carcinogenic risk' in the IARC Monographs series is taken to mean that an agent is capable of causing cancer. The Monographs evaluate cancer hazards, despite the historical presence of the word 'risks' in the title.

Inclusion of an agent in the Monographs does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a Monograph does not mean that it is not carcinogenic. Similarly, identification of cancer sites with sufficient evidence or limited evidence in humans should not be viewed as precluding the possibility that an agent may cause cancer at other sites.

The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of an agent to humans is encouraged to make this information available to the Section of IARC Monographs, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Section of IARC Monographs, so that corrections can be reported in future volumes.

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PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, the scientific principles and procedures used in developing a *Monograph*, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a *Monograph* or list of evaluations.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of chemicals, including requests for lists of known and suspected human carcinogens. It was clear that it would not be a simple task to summarize adequately the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this topic. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended '...that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented.' The IARC Governing Council adopted a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation of carcinogenic risk of chemicals to man, which became the initial title of the series.

In the succeeding years, the scope of the programme broadened as *Monographs* were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. In 1988, the phrase 'of chemicals' was dropped from the title, which assumed its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Through the *Monographs* programme, IARC seeks to identify the causes of human cancer. This is the first step in cancer prevention, which is needed as much today as when IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 (Stewart & Kleihues, 2003). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries. As a result of *Monographs* evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and in the environment.

The criteria established in 1971 to evaluate carcinogenic risks to humans were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the *Monographs* series. Those criteria were subsequently updated by further ad hoc Advisory Groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987, 1988, 1991; Vainio et al., 1992; IARC, 2005, 2006).

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of each individual Working Group.

2. Objective and scope

The objective of the programme is to prepare, with the help of international Working Groups of experts, and to publish in the form of *Monographs*, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* represent the first step in carcinogen risk assessment, which involves examination of all relevant information to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The *Monographs* may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

In this Preamble, the term 'agent' refers to any entity or circumstance that is subject to evaluation in a *Monograph*. As the scope of the programme has broadened, categories of agents now include specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioural practices, biological organisms and physical agents. This list of categories may expand as causation of, and susceptibility to, malignant disease become more fully understood.

A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

In the *Monographs*, an agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that the agent is carcinogenic. The terms 'neoplasm' and 'tumour' are used interchangeably.

The Preamble continues the previous usage of the phrase 'strength of evidence' as a matter of historical continuity, although it should be understood that *Monographs* evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991; Vainio et al., 1992; IARC, 2005, 2006; see also Part B, Sections 4 and 6). As mechanisms of carcinogenesis are elucidated, IARC convenes international scientific conferences to determine whether a broad-based consensus has emerged

on how specific mechanistic data can be used in an evaluation of human carcinogenicity. The results of such conferences are reported in IARC Scientific Publications, which, as long as they still reflect the current state of scientific knowledge, may guide subsequent Working Groups.

Although the *Monographs* have emphasized hazard identification, important issues may also involve dose–response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–response relationship. A *Monograph* may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose–response assessment.

The *Monographs* are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

3. Selection of agents for review

Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity. Mixed exposures may occur in occupational and environmental settings and as a result of individual and cultural habits (such as tobacco smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. Ad hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993, 1998 and 2003 made recommendations as to which agents should be evaluated in the *Monographs* series. Recent recommendations are available on the *Monographs* programme web site (http://monographs.iarc.fr). IARC may schedule other agents for review as it becomes aware of new scientific information or as national health agencies identify an urgent public health need related to cancer.

As significant new data become available on an agent for which a *Monograph* exists, a re-evaluation may be made at a subsequent meeting, and a new *Monograph* published. In some cases it may be appropriate to review only the data published since a prior evaluation. This can be useful for updating a database, reviewing new data to resolve a previously open question or identifying new tumour sites associated with a carcinogenic agent. Major changes in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full review.

4. Data for the *Monographs*

Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate

or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

Mechanistic and other relevant data are also reviewed. A *Monograph* does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section 4). Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered. Exceptionally, doctoral theses and other material that are in their final form and publicly available may be reviewed.

Exposure data and other information on an agent under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, published and unpublished sources of information may be considered.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description (see Part B). The reasons for not giving further consideration to an individual study also are indicated in the square brackets.

5. Meeting participants

Five categories of participant can be present at *Monograph* meetings.

(a) The Working Group

The Working Group is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans. Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.

(b) Invited Specialists

Invited Specialists are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues in the section on exposure, such as a general description of data on production and use (see Part B, Section 1). Invited Specialists do not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.

(c) Representatives of national and international health agencies

Representatives of national and international health agencies often attend meetings because their agencies sponsor the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations.

(d) Observers with relevant scientific credentials

Observers with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Attention will be given to achieving a balance of Observers from constituencies with differing perspectives. They are invited to observe the meeting and should not attempt to influence it. Observers do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after they have observed a discussion. Observers agree to respect the Guidelines for Observers at *IARC Monographs* meetings (available at http://monographs.iarc.fr).

(e) The IARC Secretariat

The IARC Secretariat consists of scientists who are designated by IARC and who have relevant expertise. They serve as rapporteurs and participate in all discussions. When requested by the meeting chair or subgroup chair, they may also draft text or prepare tables and analyses.

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine whether there is a conflict that warrants some limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume (Cogliano et al., 2004).

The names and principal affiliations of participants are available on the *Monographs* programme web site (http://monographs.iarc.fr) approximately two months before each meeting. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano et al., 2005).

All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.

6. Working procedures

A separate Working Group is responsible for developing each volume of *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year in advance of the meeting of a Working Group, the agents to be reviewed are announced on the *Monographs* programme web site (http://monographs.iarc.fr) and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed. Meeting participants who are asked to prepare preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.

For most chemicals and some complex mixtures, the major collection of data and the preparation of working papers for the sections on chemical and physical properties, on analysis, on production and use, and on occurrence are carried out under a separate contract funded by the US National Cancer Institute. Industrial associations, labour unions and other knowledgeable organizations may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. Information on production and trade is obtained from governmental, trade and market research publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available for a variety of reasons (e.g. not collected or made public in all producing countries, production is small). Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and sent, before the meeting, to Working Group Members and Invited Specialists for review.

The Working Group meets at IARC for seven to eight days to discuss and finalize the texts and to formulate the evaluations. The objectives of the meeting are peer review and consensus. During the first few days, four subgroups (covering exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review the working papers, develop a joint subgroup draft and write summaries. Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered. During the last few days, the Working Group meets in plenary session to review the subgroup drafts and develop the evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections.

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.

After the meeting, the master copy is verified by consulting the original literature, edited and prepared for publication. The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the *Monographs* programme web site soon after the meeting.

B. SCIENTIFIC REVIEW AND EVALUATION

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.

The scope of the *IARC Monographs* programme has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:

Exposure data
Studies of cancer in humans
Studies of cancer in experimental animals
Mechanistic and other relevant data
Summary
Evaluation and rationale

In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.

This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

1. Exposure data

Each *Monograph* includes general information on the agent: this information may vary substantially between agents and must be adapted accordingly. Also included is information on production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. Depending on the agent, regulations and guidelines for use may be presented.

(a) General information on the agent

For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented.

For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated.

For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.

Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.

(b) Analysis and detection

An overview of methods of analysis and detection of the agent is presented, including their sensitivity, specificity and reproducibility. Methods widely used for regulatory purposes are emphasized. Methods for monitoring human exposure are also given. No critical evaluation or recommendation of any method is meant or implied.

(c) Production and use

The dates of first synthesis and of first commercial production of a chemical, mixture or other agent are provided when available; for agents that do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided when available. In addition, methods of synthesis used in past and present commercial production and different methods of production,

which may give rise to different impurities, are described.

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

(d) Occurrence and exposure

Information on the occurrence of an agent in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases.

Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are reported. Information is presented on the range of human exposure, including occupational and environmental exposures. This includes relevant findings from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with date and place. For biological agents, the epidemiology of infection is described.

(e) Regulations and guidelines

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccination and therapy, are described.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part A, Section 4). Studies of biomarkers are included when they are relevant to an evaluation of carcinogenicity to humans.

(a) Types of study considered

Several types of epidemiological study contribute to the assessment of carcinogenicity in humans — cohort studies, case–control studies, correlation (or ecological) studies and intervention studies. Rarely, results from randomized trials may be available. Case reports and case series of cancer in humans may also be reviewed.

Cohort and case–control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of effect (such as relative risk) as the main measure of association. Intervention studies may provide strong evidence for making causal inferences, as exemplified by cessation of smoking and the subsequent decrease in risk for lung cancer.

In correlation studies, the units of investigation are usually whole populations (e.g. in

particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population to the agent under study. In correlation studies, individual exposure is not documented, which renders this kind of study more prone to confounding. In some circumstances, however, correlation studies may be more informative than analytical study designs (see, for example, the *Monograph* on arsenic in drinking-water; IARC, 2004).

In some instances, case reports and case series have provided important information about the carcinogenicity of an agent. These types of study generally arise from a suspicion, based on clinical experience, that the concurrence of two events — that is, a particular exposure and occurrence of a cancer — has happened rather more frequently than would be expected by chance. Case reports and case series usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.

The uncertainties that surround the interpretation of case reports, case series and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case–control and cohort studies, however, these types of study may add materially to the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(b) Quality of studies considered

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. Bias is the effect of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between an agent and disease. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect.

In evaluating the extent to which these factors have been minimized in an individual study, consideration is given to several aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration is given when interpreting subsequent studies that included these data in an enlarged population. Most of these considerations apply equally to case–control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

First, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Second, the authors should have taken into account — in the study design and analysis — other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may or may not be more appropriate than those with national rates. Internal comparisons of

frequency of disease among individuals at different levels of exposure are also desirable in cohort studies, since they minimize the potential for confounding related to the difference in risk factors between an external reference group and the study population.

Third, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. These methods have been reviewed for case–control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(c) *Meta-analyses and pooled analyses*

Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity, and well conducted analyses can be considered. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis) and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (Greenland, 1998).

The advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail. A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, procedures of data collection, methods of measurement and effects of unmeasured co-variates that may differ among studies. Despite these limitations, well conducted combined analyses may provide a firmer basis than individual studies for drawing conclusions about the potential carcinogenicity of agents.

IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular *Monograph* (see Part A, Section 4). Additionally, as a means of gaining insight from the results of multiple individual studies, ad hoc calculations that combine data from different studies may be conducted by the Working Group during the course of a *Monograph* meeting. The results of such original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies or de-novo analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important that the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

(d) *Temporal effects*

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal

relationships may be useful in making causal inferences. In addition, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although, at best, they allow only indirect inferences about mechanisms of carcinogenesis.

(e) Use of biomarkers in epidemiological studies

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio et al., 1992; Toniolo et al., 1997; Vineis et al., 1999; Buffler et al., 2004). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

(f) Criteria for causality

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound.

If the risk increases with the exposure, this is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

Several scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through the causation of multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and

coherence of the overall database are considered. Data on biomarkers may be employed in an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires first that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

3. Studies of cancer in experimental animals

All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species (Wilbourn et al., 1986; Tomatis et al., 1989). For several agents (e.g. aflatoxins, diethylstilbestrol, solar radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio et al., 1995). Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans. Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6).

Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (see Part A, Section 4). In all experimental settings, the nature and extent of impurities or contaminants present in the agent being evaluated are given when available. Animal species, strain (including genetic background where applicable), sex, numbers per group, age at start of treatment, route of exposure, dose levels, duration of exposure, survival and information on tumours (incidence, latency, severity or multiplicity of neoplasms or preneoplastic lesions) are reported. Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate

(e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2002).

Other studies considered may include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies, co-carcinogenicity studies and studies in genetically modified animals); studies in which the end-point was not cancer but a defined precancerous lesion; experiments on the carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory animals (e.g. livestock and companion animals) exposed to the agent.

For studies of mixtures, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery. Another consideration is that chemical and toxicological interactions of components in a mixture may alter dose–response relationships. The relevance to human exposure of the test mixture administered in the animal experiment is also assessed. This may involve consideration of the following aspects of the mixture tested: (i) physical and chemical characteristics, (ii) identified constituents that may indicate the presence of a class of substances and (iii) the results of genetic toxicity and related tests.

The relevance of results obtained with an agent that is analogous (e.g. similar in structure or of a similar virus genus) to that being evaluated is also considered. Such results may provide biological and mechanistic information that is relevant to the understanding of the process of carcinogenesis in humans and may strengthen the biological plausibility that the agent being evaluated is carcinogenic to humans (see Part B, Section 2f).

(a) Qualitative aspects

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age and duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

Considerations of importance in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route of exposure were appropriate; (iv) whether the survival of treated animals was similar to that of controls; (v) whether there were adequate numbers of animals per group; (vi) whether both male and female animals were used; (vii) whether animals were allocated randomly to groups; (viii) whether the duration of observation was adequate; and (ix) whether the data were reported and analysed adequately.

When benign tumours (a) occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) appear to represent a stage in the progression to malignancy, they are usually combined in the assessment of tumour incidence (Huff et al., 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent induces only benign neoplasms that appear to be end-points that do not readily undergo

transition to malignancy, the agent should nevertheless be suspected of being carcinogenic and requires further investigation.

(b) Quantitative aspects

The probability that tumours will occur may depend on the species, sex, strain, genetic background and age of the animal, and on the dose, route, timing and duration of the exposure. Evidence of an increased incidence of neoplasms with increasing levels of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Mechanisms such as induction of DNA damage or inhibition of repair, altered cell division and cell death rates and changes in intercellular communication are important determinants of dose–response relationships for some carcinogens. Since many chemicals require metabolic activation before being converted to their reactive intermediates, both metabolic and toxicokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce nonlinearity in the dose–response relationship (Hoel et al., 1983; Gart et al., 1986), as could saturation of processes such as DNA repair. The dose–response relationship can also be affected by differences in survival among the treatment groups.

(c) Statistical analyses

Factors considered include the adequacy of the information given for each treatment group: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto et al., 1980; Gart et al., 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether or not there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel-Haenzel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the Poly-K test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other more complicated statistical procedures may be needed (Sherman et al., 1994; Dunson et al., 2003).

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls,

particularly when historical controls show high between-study variability and are, thus, of little relevance to the current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals (Haseman et al., 1984; Fung et al., 1996; Greim et al., 2003).

Although meta-analyses and combined analyses are conducted less frequently for animal experiments than for epidemiological studies due to differences in animal strains, they can be useful aids in interpreting animal data when the experimental protocols are sufficiently similar.

4. Mechanistic and other relevant data

Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. The nature of the mechanistic and other relevant data depends on the biological activity of the agent being considered. The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited. Relevant topics may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-stages, other relevant data and other adverse effects. When data on biomarkers are informative about the mechanisms of carcinogenesis, they are included in this section.

These topics are not mutually exclusive; thus, the same studies may be discussed in more than one subsection. For example, a mutation in a gene that codes for an enzyme that metabolizes the agent under study could be discussed in the subsections on toxicokinetics, mechanisms and individual susceptibility if it also exists as an inherited polymorphism.

(a) Toxicokinetic data

Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic factors that may affect dose–response relationships include uptake, deposition, biopersistence and half-life in tissues, protein binding, metabolic activation and detoxification. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be important for the extrapolation of hazards between species and in clarifying the role of in-vitro findings.

(b) Data on mechanisms of carcinogenesis

To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. For each possible mechanism, a representative selection of key data from humans and experimental systems is summarized. Attention is given to gaps in the data and to data that suggests that more than one mechanism may be operating. The relevance of the mechanism to humans is discussed, in particular, when mechanistic data are derived from experimental model systems. Changes in the affected organs, tissues or cells can be divided into three non-exclusive levels as described below.

(i) Changes in physiology

Physiological changes refer to exposure-related modifications to the physiology and/or response of cells, tissues and organs. Examples of potentially adverse physiological changes include mitogenesis, compensatory cell division, escape from apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal hormones and changes in immune surveillance.

(ii) Functional changes at the cellular level

Functional changes refer to exposure-related alterations in the signalling pathways used by cells to manage critical processes that are related to increased risk for cancer. Examples of functional changes include modified activities of enzymes involved in the metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA repair, alterations in cyclin-dependent kinases that govern cell cycle progression, changes in the patterns of post-translational modifications of proteins, changes in regulatory factors that alter apoptotic rates, changes in the secretion of factors related to the stimulation of DNA replication and transcription and changes in gap–junction-mediated intercellular communication.

(iii) Changes at the molecular level

Molecular changes refer to exposure-related changes in key cellular structures at the molecular level, including, in particular, genotoxicity. Examples of molecular changes include formation of DNA adducts and DNA strand breaks, mutations in genes, chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater emphasis is given to irreversible effects.

The use of mechanistic data in the identification of a carcinogenic hazard is specific to the mechanism being addressed and is not readily described for every possible level and mechanism discussed above.

Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.

Tests for genetic and related effects are described in view of the relevance of gene mutation and chromosomal aberration/aneuploidy to carcinogenesis (Vainio et al., 1992; McGregor et al., 1999). The adequacy of the reporting of sample characterization is considered and, when necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The concentrations employed are given, and mention is made of whether the use of an exogenous metabolic system in vitro affected the test result. These data are listed in tabular form by phylogenetic classification.

Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information on the types of genetic effect produced and on the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g. gene mutations), while others are associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for tumour promotion, cell transformation and gap–junction intercellular communication may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. Critical appraisals of these tests have been published (Montesano et al., 1986; McGregor et al., 1999).

Genetic or other activity manifest in humans and experimental mammals is regarded to be of

greater relevance than that in other organisms. The demonstration that an agent can induce gene and chromosomal mutations in mammals in vivo indicates that it may have carcinogenic activity. Negative results in tests for mutagenicity in selected tissues from animals treated in vivo provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) (Vainio et al., 1992). Factors that may give misleading results in short-term tests have been discussed in detail elsewhere (Montesano et al., 1986; McGregor et al., 1999).

When there is evidence that an agent acts by a specific mechanism that does not involve genotoxicity (e.g. hormonal dysregulation, immune suppression, and formation of calculi and other deposits that cause chronic irritation), that evidence is presented and reviewed critically in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g. Capen et al., 1999).

For biological agents such as viruses, bacteria and parasites, other data relevant to carcinogenicity may include descriptions of the pathology of infection, integration and expression of viruses, and genetic alterations seen in human tumours. Other observations that might comprise cellular and tissue responses to infection, immune response and the presence of tumour markers are also considered.

For physical agents that are forms of radiation, other data relevant to carcinogenicity may include descriptions of damaging effects at the physiological, cellular and molecular level, as for chemical agents, and descriptions of how these effects occur. 'Physical agents' may also be considered to comprise foreign bodies, such as surgical implants of various kinds, and poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are a result of their physical presence in tissues or body cavities. Other relevant data for such materials may include characterization of cellular, tissue and physiological reactions to these materials and descriptions of pathological conditions other than neoplasia with which they may be associated.

(c) Other data relevant to mechanisms

A description is provided of any structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent, the toxicological implications of the physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

High-output data, such as those derived from gene expression microarrays, and high-throughput data, such as those that result from testing hundreds of agents for a single end-point, pose a unique problem for the use of mechanistic data in the evaluation of a carcinogenic hazard. In the case of high-output data, there is the possibility to overinterpret changes in individual end-points (e.g. changes in expression in one gene) without considering the consistency of that finding in the broader context of the other end-points (e.g. other genes with linked transcriptional control). High-output data can be used in assessing mechanisms, but all end-points measured in a single experiment need to be considered in the proper context. For high-throughput data, where the number of observations far exceeds the number of end-points measured, their utility for identifying common mechanisms across multiple agents is enhanced. These data can be used to identify mechanisms that not only seem plausible, but also have a consistent pattern of carcinogenic response across entire classes of related compounds.

(d) Susceptibility data

Individuals, populations and life-stages may have greater or lesser susceptibility to an agent, based on toxicokinetics, mechanisms of carcinogenesis and other factors. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of genes involved in the metabolism of the agent under evaluation, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for or alteration of metabolic capacity by medications or other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical exposure, a suppressed immune system, periods of higher-than-usual tissue growth or regeneration and genetic polymorphisms that lead to differences in behaviour (e.g. addiction). Such data can substantially increase the strength of the evidence from epidemiological data and enhance the linkage of in-vivo and in-vitro laboratory studies to humans.

(e) Data on other adverse effects

Data on acute, subchronic and chronic adverse effects relevant to the cancer evaluation are summarized. Adverse effects that confirm distribution and biological effects at the sites of tumour development, or alterations in physiology that could lead to tumour development, are emphasized. Effects on reproduction, embryonic and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is judged by the same criteria as those applied to epidemiological studies of cancer, but fewer details are given.

5. Summary

This section is a summary of data presented in the preceding sections. Summaries can be found on the *Monographs* programme web site (http://monographs.iarc.fr).

(a) Exposure data

Data are summarized, as appropriate, on the basis of elements such as production, use, occurrence and exposure levels in the workplace and environment and measurements in human tissues and body fluids. Quantitative data and time trends are given to compare exposures in different occupations and environmental settings. Exposure to biological agents is described in terms of transmission, prevalence and persistence of infection.

(b) Cancer in humans

Results of epidemiological studies pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized. The target organ(s) or tissue(s) in which an increase in cancer was observed is identified. Dose–response and other quantitative data may be summarized when available.

(c) Cancer in experimental animals

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species, study design and route of administration, it is stated whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or preneoplastic lesions were observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also mentioned. Negative findings, inverse relationships, dose–response and other quantitative data are also summarized.

(d) Mechanistic and other relevant data

Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and

the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are summarized. In addition, information on susceptible individuals, populations and life-stages is summarized. This section also reports on other toxic effects, including reproductive and developmental effects, as well as additional relevant data that are considered to be important.

6. Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In

addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:** The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

***Limited evidence of carcinogenicity*:** The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

***Inadequate evidence of carcinogenicity*:** The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

***Evidence suggesting lack of carcinogenicity*:** Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(c) Mechanistic and other relevant data

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics,

physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as 'weak', 'moderate' or 'strong'. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole, to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is carcinogenic to humans.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental

animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is probably carcinogenic to humans.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is possibly carcinogenic to humans.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is probably not carcinogenic to humans.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity*

in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

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GENERAL REMARKS

Part C of Volume 100 of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* contains updated assessments of arsenic, metals, fibres, and dusts that were first classified as *carcinogenic to humans (Group 1)* in Volumes 1–99.

Volume 100 – General Information

About half of the agents classified in Group 1 were last reviewed more than 20 years ago, before mechanistic studies became prominent in evaluations of carcinogenicity. In addition, more recent epidemiological studies and animal cancer bioassays have demonstrated that many cancer hazards reported in earlier studies were later observed in other organs or through different exposure scenarios. Much can be learned by updating the assessments of agents that are known to cause cancer in humans. Accordingly, IARC has selected *A Review of Human Carcinogens* to be the topic for Volume 100. It is hoped that this volume, by compiling the knowledge accumulated through several decades of cancer research, will stimulate cancer prevention activities worldwide, and will be a valued resource for future research to identify other agents suspected of causing cancer in humans.

Volume 100 was developed by six separate Working Groups:

Pharmaceuticals
Biological agents
Arsenic, metals, fibres, and dusts
Radiation
Personal habits and indoor combustions
Chemical agents and related occupations

Because the scope of Volume 100 is so broad, its *Monographs* are focused on key information. Each *Monograph* presents a description of a carcinogenic agent and how people are exposed, critical overviews of the epidemiological studies and animal cancer bioassays, and a concise review of the agent's toxicokinetics, plausible mechanisms of carcinogenesis, and potentially susceptible populations, and life-stages. Details of the design and results of individual epidemiological studies and animal cancer bioassays are summarized in tables. Short tables that highlight key results are printed in Volume 100, and more extensive tables that include all studies appear on the *Monographs* programme website (http://monographs.iarc.fr/). For a few well-established associations (for example, tobacco smoke and human lung cancer), it was impractical to include all studies, even in the website tables. In those instances, the rationale for inclusion or exclusion of sets of studies is given.

Each section of Volume 100 was reviewed by a subgroup of the Working Group with appropriate subject expertise, then all the sections of a *Monograph* were discussed together in a plenary session of the full Working Group. As a result, the evaluation statements and other conclusions reflect the views of the Working Group as a whole.

Volume 100 compiles information on tumour sites and mechanisms of carcinogenesis. This information will be used in two scientific publications that may be considered as annexes to this volume. One publication, *Tumour Site Concordance between Humans and Experimental Animals*, will analyze the correspondence of tumour sites among humans and different animal species. It will discuss the predictive value of different animal tumours for cancer in humans, and perhaps identify human tumour sites for which there are no good animal models. Another publication, *Mechanisms Involved in Human Carcinogenesis*, will describe mechanisms known to or likely to cause cancer in humans. Joint consideration of multiple agents that act through similar mechanisms should facilitate the development of a more comprehensive discussion of these mechanisms. Because susceptibility often has its basis in a mechanism, this could also facilitate a more confident and precise description of populations that may be susceptible to agents acting through each mechanism. This publication will also suggest biomarkers that could improve the design of future studies. In this way, IARC hopes that Volume 100 will serve to improve the design of future cancer studies.

Specific remarks about the review of pharmaceutical agents in this volume

1. Arsenic and metals

One issue for several of these agents was the designation of the agent classified as carcinogenic. Arsenic and the metals considered exist in several oxidation states and in different forms that have different chemical and physical properties: metallic/elemental forms, alloys, and multiple compounds. For arsenic and the metals, the Working Group needed to consider whether:

1) the metallic/elemental form itself is carcinogenic;
2) the metallic/elemental form and the compounds are carcinogenic; or
3) only certain compounds are carcinogenic.

The simultaneous review of arsenic and multiple metals in this volume offered the opportunity for the Working Group to address the designation of these elements and/or their compounds in a uniform fashion. There had been some lack of consistency in prior designations, in part reflecting the nature of the evidence available and precedents in terminology around specific elements. Arsenic, for example, is widely referred to as “arsenic” alone and not as “arsenic and arsenic compounds.”

In the *Monograph* on nickel and nickel compounds, the Working Group phrased its evaluation of the epidemiological studies as “mixtures of nickel compounds and nickel metal.” The overall evaluation, however, was constrained to cover only nickel compounds and not nickel metal, in accordance with IARC’s previously announced plan that Volume 100 would evaluate agents that had been classified as *carcinogenic to humans (Group 1)* in Volumes 1–99, and only nickel compounds had been classified in Group 1 in Volume 49 (IARC, 1990). Based on the previous evaluation in Volume 49, nickel metal remains classified as *possibly carcinogenic to humans (Group 2B)*. The Working Group

recommends that there is a need for IARC to re-evaluate nickel metal in the near future in the context of the review of nickel compounds in this volume.

The situation was similar for chromium in that the review in Volume 100 considered the carcinogenicity of chromium (VI), but not of chromium with other oxidation states. The decision to omit metallic chromium or chromium (III) compounds from present assessment should not be interpreted as implying that these compounds are not carcinogenic or that the current evidence base is unchanged from that at the time of Volume 49 (IARC, 1990). Indeed, the evidence base has expanded and the Working Group does not pre-judge what the results of a new evaluation might be.

In the *Monograph* on arsenic and arsenic compounds, the Working Group developed a single updated assessment of agents that had been evaluated in previous *Monograph*s on arsenic and arsenic compounds (Volume 23 and Supplement 7, IARC, 1980, 1987a), arsenic in drinking-water (Volume 84, IARC, 2004), and gallium arsenide (Volume 86, IARC, 2006). It should be understood that arsenic in drinking-water and gallium arsenide should continue to be regarded as *carcinogenic to humans*, covered in this volume by the evaluation of arsenic and inorganic arsenic compounds.

In interpreting the human evidence on these agents, a particular difficulty was posed by the mixed exposures sustained by the worker populations included in the cohort studies. For groups exposed simultaneously to an agent in elemental/metallic form and to its compounds, the evidence may be uninformative as to the components of the mixture that cause cancer. When the evidence comes only from mixed exposure circumstances, the Working Group considered that the evaluation should be phrased as referring to "exposure to the element and its compounds."

This phrasing should not be interpreted as meaning that:

1) separate human evidence is available for the metallic/elemental form itself and for each of its compounds or

2) the evaluation of human evidence applies separately to the metallic/elemental form and to each of its compounds.

From the human evidence, insight can be gained as to the specific carcinogenic agent if sufficient informative studies are available on multiple cohorts having exposures to differing speciations of the element. Additionally, cancer bioassay and mechanistic evidence are critical to determining which components of the exposure mixture are carcinogenic, and were given full consideration by the Working Group.

2. Fibres and Dusts

When an agent is referred to as a dust, the assumption made by the Working Group was that the major route of exposure was by inhalation.

The assessment of toxicity and carcinogenicity of poorly soluble materials in the form of particles or fibres is difficult for the following reasons:

First, chemical composition alone does not fully define the relevant biological properties of particulate materials.

Second, particulate and fibrous carcinogens may undergo more complex metabolic transformation than other chemical agents. The surface of dusts may be modified *in vivo*, for example, there may be removal or deposition of metal ions or protein adsorption. These *in vivo* modifications may alter potency of the native particles or fibres.

Third, when comparing potency of dust particles, surface area may be a more appropriate dose metric than mass. In many cases, the extent of particle-derived free radicals and release of inflammatory mediators and the subsequent biological response correlate with surface area.

Fourth, particles and fibres with low solubility including quartz and asbestos fibres induce toxicity in the particulate form and not as individual molecules or ions. Particles and fibres may be deposited and retained in a focal area for a long time and contribute to the induction of lesions at this site. Particles and fibres may also be translocated to extrapulmonary sites.

Two occupations previously classified in Group 1 are considered in this volume. Boot and shoe manufacture and repair was previously evaluated in Volume 25 and in Supplement 7 (IARC, 1981, 1987a). In this volume, the Working Group concluded that the nasal sinus tumours and leukaemias observed in the epidemiological studies could be attributed to exposure to leather dust and to benzene, respectively. In accordance with the Preamble (see part B, Section 6a), the Working Group focused its evaluation more narrowly on leather dust, after searching for other studies involving this new agent. The Working Group renamed this *Monograph* "Leather Dust." (The *Monograph* on Benzene will be updated in Part F of Volume 100.)

Furniture and cabinet making was also previously evaluated in Volume 25 and in Supplement 7 (IARC, 1981, 1987a). In this volume, the Working Group concluded that the tumours of the nasal sinus and nasopharynx observed in the epidemiological studies could be attributed to exposure to wood dust or formaldehyde. Accordingly, these studies are reviewed in this volume in the *Monograph* on Wood Dust. (The *Monograph* on Formaldehyde will also be updated in Part F of Volume 100.)

The previous *IARC Monographs* on Talc Containing Asbestiform Fibres (Volume 42 and Supplement 7, IARC, 1987a, b) concerned talc described as containing asbestiform tremolite and anthophyllite. These fibres fit the definition of asbestos and therefore a separate review of talc containing asbestiform fibres was not undertaken. The studies on talc containing asbestiform fibres were considered when developing the *Monograph* on asbestos. Talc containing asbestos as well as other mixtures containing asbestos should be regarded as *carcinogenic to humans*.

In evaluating the carcinogenicity of asbestos fibres, the Working Group evaluated experimental data using the six types of asbestos fibres (Chrysotile, Amosite, Crocidolite, Tremolite, Actinolite and Anthophyllite) and erionite based on *in vitro* cellular assays and/or cancer bioassays. It should be understood that minerals containing asbestos in any form should be regarded as *carcinogenic to humans*. The Working Group agreed that the most important physicochemical properties of asbestos fibres relevant for toxicity and carcinogenicity are surface chemistry and reactivity, surface area, fibre dimensions, and biopersistence. Extrapolation of toxicity to other crystalline mineral fibres should not be done in the absence of epidemiological or experimental data based on *in vitro* and *in vivo* assays.

The toxicity of crystalline silica dusts obtained from different sources may be related to their geological history, process of particle formation, modifications during mining, processing and use, or surface contaminants even in trace amounts. Freshly ground crystalline silica exhibits a higher toxic potential than aged dusts. Crystalline silica may occur embedded in clays and other minerals or may be mixed with other materials in commercial products. It is possible that these other minerals or materials may adsorb onto the surface of crystalline silica dust and modify its reactivity. However, the extent of surface coverage and the potency of these modified dusts after residence in the lungs have not been systematically assessed.

3. Cross-cutting issues

3.1 Epidemiology

The epidemiological evidence considered in this Volume largely comes from studies of worker groups exposed to the agents under consideration. Additionally, population-based case–control studies also supply relevant evidence as do a few case series. There are several general issues related to these lines of epidemiological evidence that are covered in these comments.

The epidemiological evidence considered in this Volume largely comes from studies of worker groups exposed to the agents under consideration at levels that were high in relation to contemporary exposures, particularly in more developed countries. The cohort studies of workers have the general design of longitudinal follow-up of groups known to be exposed to the agent of interest in their workplace. Some cohort studies incorporate specific, unexposed comparison populations whereas others make a comparison to the rates of mortality in the general population, typically at the national level but sometimes on smaller geographic domains, e.g. states or counties. The measures of association used (e.g. standardized mortality ratios or SMRs) compare the rate of outcome in the exposed population to that in the unexposed population. One general concern in interpreting these measures of association is the appropriateness of the comparison population selected. National rates are often used because they are available and stable, but use of such rates may be inappropriate if there are important differences between the study population and the population at large on factors that might confound or modify the relationship between exposure and outcome. With appropriate consideration, local rates may be more suitable because factors that may confound the relationship between cancer risk and exposure, e.g. cigarette smoking, are likely to be more similar than a national population to the distributions in the worker population. Use of both national and local rates provides a sensitivity analysis as to the potential role of confounding. However, use of local rates may introduce bias if they are influenced by occupational or environmental exposures resulting from the plants under study, or if the geographical areas available for analyses do not reflect the areas from which the occupational population as drawn. Use of local rates may also result in imprecision of the epidemiological risk estimate due to instability resulting from small numbers and/or inaccuracies in small area data. The most appropriate comparison group would be other worker populations.

The informativeness of a cohort study depends on its size, i.e. the numbers of participants and outcome events. The sample sizes of the various cohort studies reflect the numbers of workers employed during the period of interest. Many of the studies had small population sizes, leading to imprecise measures of association, i.e. with wide confidence intervals. For some agents, small studies were set aside because they were uninformative. The Working Group did not attempt to combine the results of all studies, regardless of size, using quantitative meta-analysis.

3.2 Mixed exposures

In many of the cohorts studied, the workers were exposed to mixtures generated by industrial processes that contained not only the agent(s) of concern, but other potentially carcinogenic agents as well. For example, in some populations exposed to chromium, there was simultaneous exposure to arsenic. In analyses of the data from such studies, efforts were made to separate the effect of the agent of concern from the effects of other, potentially confounding agents. Such disentanglement is

possible only if the exposures are not highly correlated and the requisite data on exposures to the agents are available. There is also the assumption underlying such analyses that the effects of the various agents in the mixture are independent. In its deliberations, the Working Group recognized that exposures to many of the agents took place through exposures to mixtures containing them and took this into account in its interpretation of the evidence.

Exposures were estimated for study participants using approaches that typically were based on measurements and reconstruction of exposures based on work history and job–exposure matrices. Additionally, duration of employment was used as a surrogate for exposure. The measures of exposure were used in analyses directed at characterizing exposure–response relationships. Given the limited data available for estimating exposures, the exposure measures were subject to some degree of misclassification, likely random. One consequence of such exposure misclassification would be a blunting of estimated exposure–response relationships.

3.3 Smoking as confounder

In interpreting findings related to lung cancer and other sites for which smoking is a cause, there is the potential for confounding by smoking, particularly because many studies lacked information on smoking and direct adjustment for smoking was not possible. In assessing the potential for confounding by smoking, consideration was given to whether internal comparisons were made, which should not be as likely to be confounded as external comparisons. Additionally, some studies used available smoking information to estimate the potential for confounding by smoking. Such analyses are useful but have the underlying assumption that the effects of smoking and the agent of interest are independent.

Since the prior reviews, several data sets had undergone re-analysis by analysts who were not the original investigators. As appropriate, the Working Group considered these re-analyses to assess any insights into the original analyses.

A summary of the findings of this volume appears in The Lancet Oncology (Straif et al., 2009).

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ARSENIC AND ARSENIC COMPOUNDS

Arsenic and arsenic compounds were considered by previous IARC Working Groups in 1979, 1987, and 2002 (IARC, 1980, 1987, 2004). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Information on the physical and chemical properties of arsenic and arsenic compounds can be found in Table 1.1, for further details please refer to IARC (1980). The list is not exhaustive, nor does it comprise necessarily the most commercially important arsenic-containing substances; rather, it indicates the range of arsenic compounds available.

1.2 Chemical and physical properties of the agents

Arsenic (atomic number, 33; relative atomic mass, 74.92) has chemical and physical properties intermediate between a metal and a non-metal, and is often referred to as a metalloid or semi-metal. It belongs to Group VA of the Periodic Table, and can exist in four oxidation states: –3, 0, +3, and +5. Arsenite, As^{III}, and arsenate, As^{V}, are the predominant oxidation states under, respectively, reducing and oxygenated conditions (WHO, 2001; IARC, 2004).

From a biological and toxicological perspective, there are three major groups of arsenic compounds:

-inorganic arsenic compounds,

-organic arsenic compounds, and

-arsine gas.

Of the inorganic arsenic compounds, arsenic trioxide, sodium arsenite and arsenic trichloride are the most common trivalent compounds, and arsenic pentoxide, arsenic acid and arsenates (e.g. lead arsenate and calcium arsenate) are the most common pentavalent compounds. Common organic arsenic compounds include arsanilic acid, methylarsonic acid, dimethylarsinic acid (cacodylic acid), and arsenobetaine (WHO, 2000).

1.3 Use of the agents

Arsenic and arsenic compounds have been produced and used commercially for centuries. Current and historical uses of arsenic include pharmaceuticals, wood preservatives, agricultural chemicals, and applications in the mining, metallurgical, glass-making, and semiconductor industries.

Arsenic was used in some medicinal applications until the 1970s. Inorganic arsenic was used

Table 1.1 Chemical names, CAS numbers, synonyms, and molecular formulae of arsenic and arsenic compounds

Chemical name	CAS Reg. No.	Synonyms	Formula
Arsanilic acid	98-50-0	Arsonic acid, (4-aminophenyl)-	$C_6H_8AsNO_3$
Arsenic[a]	7440-38-2	Metallic arsenic	As
Arsenic(V) pentoxide[b]	1303-28-2	Arsenic oxide [As_2O_5]	As_2O_5
Arsenic(III) sulfide	1303-33-9	Arsenic sulfide [As_2S_3]	As_2S_3
Arsenic(III) trichloride	7784-34-1	Arsenic chloride [$AsCl_3$]	$AsCl_3$
Arsenic(III) trioxide[a,c]	1327-53-3	Arsenic oxide [As_2O_3]	As_2O_3
Arsenobetaine	64436-13-1	Arsonium, (carboxymethyl) trimethyl-, hydroxide, inner salt; 2-(trimethylarsonio)acetate	$C_5H_{11}AsO_2$
Arsine	7784-42-1	Arsenic hydride	AsH_3
Calcium arsenate	7778-44-1	Arsenic acid [H_3AsO_4] calcium salt (2:3)	$(AsO_4)_2.3Ca$
Dimethylarsinic acid	75-60-5	Cacodylic acid	$C_2H_7AsO_2$
Lead arsenate	7784-40-9	Arsenic acid [H_3AsO_4], lead (2+) salt (1:1)	$HAsO_4.Pb$
Methanearsonic acid, disodium salt	144-21-8	Arsonic acid, methyl-, disodium salt	$CH_3AsO_3.2Na$
Methanearsonic acid, monosodium salt	2163-80-6	Arsonic acid, methyl-, monosodium salt	$CH_4AsO_3.Na$
Potassium arsenate[d]	7784-41-0	Arsenic acid [H_3AsO_4], monopotassium salt	$H_2AsO_4.K$
Potassium arsenite	13464-35-2	Arsenous acid, potassium salt	$AsO_2.K$
Sodium arsenate[e]	7631-89-2	Arsenic acid, [H_3AsO_4], monosodium salt	$H_2AsO_4.Na$
Sodium arsenite	7784-46-5	Arsenous acid, sodium salt	$AsO_2.Na$
Sodium cacodylate	124-65-2	Arsinic acid, dimethyl-, sodium salt	$C_2H_6AsO_2.Na$

[a] As_2O_3 is sometimes erroneously called ‘arsenic’.
[b] The name ‘arsenic acid’ is commonly used for As_2O_5 as well as for the various hydrated products (H_3AsO_4, $H_4As_2O_7$).
[c] As_2O_3 is sometimes called ‘arsenic oxide’, but this name is more properly used for As_2O_5.
[d] The other salts, K_3AsO_4 and K_2HAsO_4, do not appear to be produced commercially.
[e] The name ‘sodium arsenate’ is also applied to both the disodium [7778-43-0] and the trisodium [13464-38-5] salts; it is therefore not always possible to determine which substance is under discussion.

in the treatment of leukaemia, psoriasis, and chronic bronchial asthma, and organic arsenic was used in antibiotics for the treatment of spirochetal and protozoal disease (ATSDR, 2007).

Inorganic arsenic is an active component of chromated copper arsenate, an antifungal wood preservative used to make “pressure-treated” wood for outdoor applications. Chromated copper arsenate is no longer used in residential applications, following a voluntary ban on its use in Canada and the United States of America at the end of 2003.

In the agricultural industry, arsenic has historically been used in a range of applications, including pesticides, herbicides, insecticides, cotton desiccants, defoliants, and soil sterilants. Inorganic arsenic pesticides have not been used for agricultural purposes in the USA since 1993. Organic forms of arsenic were constituents of some agricultural pesticides in the USA. However, in 2009, the US Environmental Protection Agency issued a cancellation order to eliminate and phase out the use of organic arsenical pesticides by 2013 (EPA, 2009). The one exception to the order is monosodium methanearsonate (MSMA), a broadleaf weed herbicide, which will continue to be approved for use on cotton. Small amounts of disodium methanearsonate (DSMA, or cacodylic acid) were historically applied to cotton fields as herbicides, but its use is now prohibited under the aforementioned US EPA 2009 organic arsenical product cancellation. Other organic

arsenicals (e.g. roxarsone, arsanilic acid and its derivatives) are used as feed additives for poultry and swine to increase the rate of weight gain, to improve feed efficiencies, pigmentation, and disease treatment and prevention (EPA, 2000, 2006; FDA, 2008a, b).

Arsenic and arsenic compounds are used for a variety of other industrial purposes. Elemental arsenic is used in the manufacture of alloys, particularly with lead (e.g. in lead acid batteries) and copper. Gallium arsenide and arsine are widely used in the semiconductor and electronics industries. Because of its high electron mobility, as well as light-emitting, electromagnetic and photovoltaic properties, gallium arsenide is used in high-speed semiconductor devices, high-power microwave and millimetre-wave devices, and opto-electronic devices, including fibre-optic sources and detectors (IARC, 2006). Arsine is used as a doping agent to manufacture crystals for computer chips and fibre optics.

Arsenic and arsenic compounds are used in the manufacture of pigments, sheep-dips, leather preservatives, and poisonous baits. They are also used in catalysts, pyrotechnics, antifouling agents in paints, pharmaceutical substances, dyes and soaps, ceramics, alloys (automotive solder and radiators), and electrophotography.

Historically, the USA has been the world's largest consumer of arsenic. Prior to 2004, about 90% of the arsenic consumed, as arsenic trioxide, was in the manufacture of wood preservatives. Since the voluntary ban on chromated copper arsenate in residential applications came into effect at the end of 2003, the consumption of arsenic for wood preservation has declined, dropping to 50% in 2007 (USGS, 2008). During 1990–2002, approximately 4% of arsenic produced was used in the manufacture of glass, and 1–4% was used in the production of non-ferrous alloys (NTP, 2005).

1.4 Environmental occurrence

Arsenic is the 20th most common element in the earth's crust, and is emitted to the environment as a result of volcanic activity and industrial activities. Mining, smelting of non-ferrous metals and burning of fossil fuels are the major anthropogenic sources of arsenic contamination of air, water, and soil (primarily in the form of arsenic trioxide). The historical use of arsenic-containing pesticides has left large tracts of agricultural land contaminated. The use of arsenic in the preservation of timber has also led to contamination of the environment (WHO, 2000, 2001).

1.4.1 Natural occurrence

In nature, arsenic occurs primarily in its sulfide form in complex minerals containing silver, lead, copper, nickel, antimony, cobalt, and iron. Arsenic is present in more than 200 mineral species, the most common of which is arsenopyrite. Terrestrial abundance of arsenic is approximately 5 mg/kg, although higher concentrations are associated with sulfide deposits. Sedimentary iron and manganese ores as well as phosphate-rock deposits occasionally contain levels of arsenic up to 2900 mg/kg (WHO, 2001).

1.4.2 Air

Arsenic is emitted to the atmosphere from both natural and anthropogenic sources. Approximately one-third of the global atmospheric flux of arsenic is estimated to be from natural sources (7900 tonnes per year). Volcanic activity is the most important natural contributor, followed by low-temperature volatilization, exudates from vegetation, and windblown dusts. Anthropogenic sources are estimated to account for nearly 24000 tonnes of arsenic emitted to the global atmosphere per year. These emissions arise from the mining and smelting of base metals, fuel combustion (e.g. waste and low-grade brown

coal), and the use of arsenic-based pesticides (WHO, 2000, 2001).

Arsenic is present in the air of suburban, urban, and industrial areas mainly as inorganic particulate (a variable mixture of As^{III} and As^{V}, with the pentavalent form predominating). Methylated arsenic is assumed to be a minor component of atmospheric arsenic (WHO, 2000). Mean total arsenic concentrations in air range from 0.02–4 ng/m^3 in remote and rural areas, and from 3–200 ng/m^3 in urban areas. Much higher concentrations (> 1000 ng/m^3) have been measured in the vicinity of industrial sources, such as non-ferrous metal smelters, and arsenic-rich coal-burning power plants (WHO, 2001).

1.4.3 Water

Arsenic, from both natural and anthropogenic sources, is mainly transported in the environment by water. The form and concentration of arsenic depends on several factors, including whether the water is oxygenated (for example, arsenites predominate under reducing conditions such as those found in deep well-waters), the degree of biological activity (which is associated with the conversion of inorganic arsenic to methylated arsenic acids), the type of water source (for example, open ocean seawater versus surface freshwater versus groundwater), and the proximity of the water source to arsenic-rich geological formations and other anthropogenic sources (WHO, 2000, 2001).

The concentration of arsenic in surface freshwater sources, like rivers and lakes, is typically less than 10 μg/L, although it can be as high as 5 mg/L near anthropogenic sources. Concentrations of arsenic in open ocean seawater and groundwater average 1–2 μg/L, although groundwater concentrations can be up to 3 mg/L in areas with volcanic rock and sulfide mineral deposits (WHO, 2001).

Exposure to high levels of arsenic in drinking-water has been recognized for many decades in some regions of the world, notably in the People's Republic of China, Taiwan (China), and some countries in Central and South America. More recently, several other regions have reported having drinking-water that is highly contaminated with arsenic. In most of these regions, the drinking-water source is groundwater, naturally contaminated from arsenic-rich geological formations. The primary regions where high concentrations of arsenic have been measured in drinking-water include large areas of Bangladesh, China, West Bengal (India), and smaller areas of Argentina, Australia, Chile, Mexico, Taiwan (China), the USA, and Viet Nam. In some areas of Japan, Mexico, Thailand, Brazil, Australia, and the USA, mining, smelting and other industrial activities have contributed to elevated concentrations of arsenic in local water sources (IARC, 2004).

Levels of arsenic in affected areas may range from tens to hundreds or even thousands of micrograms per litre, whereas in unaffected areas, levels are typically only a few micrograms per litre. Arsenic occurs in drinking-water primarily as As^{V}, although in reducing environments significant concentrations of As^{III} have also been reported. Trace amounts of methylated arsenic species are typically found in drinking-water, and higher levels are found in biological systems. More complete data on arsenic in water may be found in the previous *IARC Monograph* (IARC, 2004).

1.4.4 Soil and sediments

Natural and anthropogenic sources contribute to the levels of arsenic found in soil and sediments. Mean background concentrations in soil are often around 5 mg/kg, but can range from as low as 1 mg/kg to as high as 40 mg/kg. This variation in levels of naturally occurring arsenic in soils is associated with the presence of geological formations (e.g. sulfide ores, mineral sediments beneath peat bogs). Soils contaminated with arsenic from anthropogenic sources (e.g. mine/

smelter wastes, agricultural land treated with arsenical pesticides) can have concentrations of arsenic up to several grams per kilogram. Mean sediment arsenic concentrations range from 5–3000 mg/kg, with the higher levels occurring in areas of anthropogenic contamination (WHO, 2001).

1.5 Human exposure

1.5.1 Exposure of the general population

The primary route of arsenic exposure for the general population is via the ingestion of contaminated food or water. The daily intake of total arsenic from food and beverages is generally in the range of 20–300 µg/day.

Inhalation of arsenic from ambient air is generally a minor exposure route for the general population. Assuming a breathing rate of 20 m^3/day, the estimated daily intake may amount to about 20–200 ng in rural areas, 400–600 ng in cities without substantial industrial emission of arsenic, about 1 µg/day in a non-smoker and more in polluted areas, and up to approximately 10 µg/day in a smoker (WHO, 2000, 2001).

1.5.2 Occupational exposure

Inhalation of arsenic-containing particulates is the primary route of occupational exposure, but ingestion and dermal exposure may be significant in particular situations (e.g. during preparation of timber treated with chromated copper arsenate). Historically, the greatest occupational exposure to arsenic occurred in the smelting of non-ferrous metal, in which arseniferous ores are commonly used. Other industries or industrial activities where workers are or were exposed to arsenic include: coal-fired power plants, battery assembly, preparation of or work with pressure-treated wood, glass-manufacturing, and the electronics industry. Estimates of the number of workers potentially exposed to arsenic and arsenic compounds have been developed by the NIOSH in the USA and by CAREX in Europe. Based on the National Occupation Exposure Survey (NOES), conducted during 1981–83, NIOSH estimated that 70000 workers, including approximately 16000 female workers, were potentially exposed to arsenic and arsenic compounds in the workplace (NIOSH, 1990). Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX (CARcinogen EXposure) database estimated that 147569 workers were exposed to arsenic and arsenic compounds in the European Union, with over 50% of workers employed in the non-ferrous base metal industries (n = 40426), manufacture of wood and wood and cork products except furniture (n = 33959), and construction (n = 14740). CAREX Canada estimates that 25000 Canadians are exposed to arsenic in their workplaces (CAREX Canada, 2011). These industries include: sawmills and wood preservation, construction, farms, non-ferrous metal (except aluminium) production and processing, iron and steel mills and ferro-alloy manufacturing, oil and gas extraction, metal ore mining, glass and glass-product manufacturing, semiconductor manufacturing, and basic chemical manufacturing.

1.5.3 Dietary exposure

Low levels of inorganic and organic arsenic have been measured in most foodstuffs (typical concentrations are less than 0.25 mg/kg). Factors influencing the total concentration of arsenic in food include: food type (e.g. seafood versus meat or dairy), growing conditions (e.g. soil type, water, use of arsenic-containing pesticides), and food-processing techniques. The highest concentrations of arsenic have been found in seafood (2.4–16.7 mg/kg in marine fish, 3.5 mg/kg in mussels, and more than 100 mg/kg in certain crustaceans), followed by meats, cereals, vegetables, fruit, and dairy products. Inorganic arsenic

is the predominant form found in meats, poultry, dairy products and cereal, and organic arsenic (e.g. arsenobetaine) predominates in seafood, fruit, and vegetables (WHO, 2000, 2001).

Regional differences are seen in the daily intake of total arsenic through food, and are mainly attributable to variations in the quantity of seafood consumed. For example, the daily dietary intake of total arsenic in Japan is higher than that in Europe and the USA (WHO, 2000). Based on the limited data available, it is estimated that approximately 25% of daily dietary arsenic intake is from inorganic sources. Arsenic intake is typically higher in men than it is in women and children, with estimated levels ranging from 1.3 μg/day for infants under 1 year of age, 4.4 μg/day for 2-year olds, 9.9 μg/day for 25–30-year-old men, 10 μg/day for 60–65-year-old women, and 13 μg/day for 60–65-year-old men (WHO, 2001).

1.5.4 Biomarkers of exposure

Arsine generation atomic absorption spectrometry (AAS) is the method of choice for biological monitoring of exposure to inorganic arsenic (WHO, 2000). The absorbed dose of arsenic can be identified and quantified in hair, nail, blood or urine samples. Because arsenic accumulates in keratin-rich tissue, total arsenic levels in hair, fingernails or toenails are used as indicators of past exposures. In contrast, because of its rapid clearing and metabolism, blood arsenic, urine arsenic, and urine arsenic metabolites (inorganic arsenic, monomethylarsonic acid [MMA^V] and dimethylarsinic acid [DMA^V]) are typically used as indicators of recent exposure.

The concentration of metabolites of inorganic arsenic in urine generally ranges from 5–20 μg/L, but may exceed 1000 μg/L (WHO, 2001). Time-weighted average (TWA) occupational exposure to airborne arsenic trioxide is significantly correlated with the inorganic arsenic metabolites in urine collected immediately after a shift or just before the next shift. For example, at an airborne concentration of 50 μg/m^3, the mean concentration of arsenic derived from the sum of the three inorganic arsenic metabolites in a post-shift urine sample was 55 μg/g of creatinine. In non-occupationally exposed subjects, the sum of the concentration of the three metabolites in urine is usually less than 10 μg/g of creatinine (WHO, 2000).

2. Cancer in Humans

The epidemiological evidence on arsenic and cancer risk comes from two distinct lines of population studies, characterized by the medium of exposure to arsenic. One set of studies addresses the cancer risk associated with inhalation. These studies involve populations that are largely worker groups who inhaled air contaminated by arsenic and other agents, as a consequence of various industrial processes. The second set of studies was carried out in locations where people ingested arsenic in drinking-water at high concentrations over prolonged periods of time.

2.1 Types of human exposure circumstances studied

2.1.1 Arsenic exposure by inhalation

The cohort studies and nested case–control studies considered in this *Monograph* that are relevant to airborne arsenic include workers in metal smelters and refineries, and miners of various ores. Case–control studies within the general population addressed occupational exposures more generally. Consequently, the exposure to inhaled arsenic was accompanied by exposures to other potentially toxic and carcinogenic by-products of combustion, such as sulfur oxides with copper smelting, polycyclic aromatic hydrocarbons, and particulate matter.

Most studies did not attempt to estimate separately exposures to the full set of agents in the inhaled mixtures, leaving open the possibility of some confounding or modification of the effect of arsenic by synergistic interactions.

2.1.2 Arsenic exposure by ingestion

For most human carcinogens, the major source of evidence contributing to causal inferences arises from case–control and cohort studies. In contrast, for arsenic in drinking-water, ecological studies provide important information on causal inference, because of the large exposure contrasts and the limited population migration. For arsenic, ecological estimates of relative risk are often so high that potential confounding with known causal factors could not explain the results. Although food may also be a source of some ingested arsenic, in several regions of the world where the concentrations of arsenic in drinking-water is very high, arsenic intake through food consumption contributes a relatively small cancer risk to the local residents (Liu *et al.*, 2006a).

The strongest evidence for the association of human cancer with arsenic in drinking-water comes from studies in five areas of the world with especially elevated levels of naturally occurring arsenic: south-western and north-eastern Taiwan (China), northern Chile, Cordoba Province in Argentina, Bangladesh, West Bengal (India), and other regions in the Ganga plain. Although data contributing to our understanding also come from many other places, the current review is largely restricted to the major studies from these regions. Some of the oral exposure may occur via seafood. However, no epidemiological studies were available with regard to the cancer risk associated with arsenic exposure via seafood, in which arsenic may occur as particular organic compounds such as arsenobetaine and arsenocholine.

(a) Taiwan (China)

Exposure to arsenic was endemic in two areas of Taiwan (China): The south-western coastal area (Chen *et al.*, 1985), and the north-eastern Lanyang Basin (Chiou *et al.*, 2001). Residents in the south-western areas drank artesian well-water with high concentrations of arsenic from the early 1910s to the late 1970s, with levels mostly above 100 µg/L (Kuo, 1968; Tseng *et al.*, 1968). In the Lanyang Basin, residents used arsenic-contaminated water from household tube wells starting in the late 1940s. Arsenic in the water of 3901 wells, tested in 1991–94 ranged from undetectable (< 0.15 µg/L) to 3.59 mg/L (median = 27.3 µg/L) (Chiou *et al.*, 2001).

(b) Northern Chile

The population-weighted average concentration of arsenic in drinking-water in Region II, an arid region of northern Chile, was about 570 µg/L over 15 years (1955–69) (Smith *et al.*, 1998). With the introduction of a water-treatment plant in 1970, levels decreased. By the late 1980s, arsenic levels in drinking-water had decreased to less than 100 µg/L in most places. With minor exceptions, water sources elsewhere in Chile have had low concentrations of arsenic (less than 10 µg/L) (Marshall *et al.*, 2007).

(c) Cordoba Province, Argentina

Of the 24 counties in Cordoba Province, two have been characterized as having elevated exposure to arsenic in drinking-water (average level, 178 µg/L), six as having medium exposure, and the remaining 16 rural counties as having low exposure (Hopenhayn-Rich *et al.*, 1996, 1998).

(d) Bangladesh, West Bengal (India), and other locations in the Ganga plain

Millions of tube wells were installed in West Bengal (India), Bangladesh, and other regions in the Ganga plain of India and Nepal starting in the late 1970s to prevent morbidity and mortality

from gastrointestinal disease (Smith *et al.*, 2000). Elevated arsenic in wells in Bangladesh was confirmed in 1993 (Khan *et al.*, 1997). In a Bangladesh survey by the British Geological Survey of 2022 water samples in 41 districts, 35% were found to have arsenic levels above 50 µg/L, and 8.4% were above 300 µg/L, with an estimate of about 21 million persons exposed to arsenic concentrations above 50 µg/L (Smith *et al.*, 2000).

2.2 Cancer of the lung

2.2.1 Exposure via inhalation

Several ecological studies were conducted on populations exposed to arsenic through industrial emissions. The worker studies primarily provide information on lung cancer. The case–control studies are also mostly directed at lung cancer, with one on non-melanoma skin cancer (see Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.1.pdf).

The cohort studies reviewed previously and here consistently show elevated lung cancer risk in the various arsenic-exposed cohorts compared with the general population or other comparison groups, with most values in the range of 2–3 (see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.2.pdf and Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.3.pdf).

The studies incorporate diverse qualitative and quantitative indices of exposure that include measures of average airborne concentration of exposure, cumulative exposure across the work experience, and duration of exposure. There is consistent evidence for a positive exposure–response relationship between the indicators of exposure and lung cancer risk. Case–control studies nested within occupational cohorts provided similar evidence with regard to exposure–response relationships.

Several analyses further explored the relationship between arsenic exposure and lung cancer risk using models based on either empirical, i.e. descriptive, or biological data (see Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.4.pdf).

Using data from the Tacoma, Washington smelter workers, Enterline *et al.* (1987) modelled the relationship between lung cancer risk and airborne arsenic exposure using power functions, and found that the exposure–response relationship was steeper at lower concentrations than shown in conventional analyses, and was concave downwards at higher concentrations. By contrast, the relationship of risk with urine arsenic concentration was linear. Lubin *et al.* (2000, 2008) analysed the exposure–response relationship of lung cancer risk with arsenic exposure in the cohort of Montana smelter workers, now followed for over 50 years. Overall, a linear relationship of risk with cumulative exposure was found; however, the slope of the relationship increased with the average concentration at which exposure had taken place, that is, the effect of a particular cumulative exposure was greater if received at a faster rate.

For a comparison of the different studies, see Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.5.pdf.

2.2.2 Exposure via ingestion

A summary of the findings of epidemiological studies on arsenic in drinking-water and risk for lung cancer are shown in Table 2.6 (water exposures) available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.6.pdf, and online Tables 2.1 to 2.4 (air exposures).

(a) Ecological studies

Ecological studies, based on mortality records, were conducted in the arseniasis endemic area of south-western Taiwan (China) (Chen *et al.*, 1985, 1988a; Wu *et al.*, 1989; Chen & Wang, 1990; Tsai *et al.*, 1999). All studies found elevated risks for lung cancer mortality associated with levels of arsenic in drinking-water, or surrogate measurements.

In Chile, Rivara *et al.* (1997) found an elevated relative risk (RR) for mortality from lung cancer in 1976–92 in Region II compared with Region VIII, a low-exposure area. Smith *et al.* (1998) found an elevated standardized mortality ratio (SMR) of approximately 3 for lung cancer for both sexes in Region II, using the national rate as standard. In Cordoba Province, Argentina, significant increases in lung cancer mortality were associated with increasing exposure to arsenic (Hopenhayn-Rich *et al.*, 1998). Smith *et al.* (2006) found an elevated lung cancer mortality (RR, 7.0; 95%CI: 5.4–8.9) among the 30–49-year-old residents of Antofagasta and Mejillones born in the period 1950–57, just before the period of exposure to high arsenic levels (1958–70). They were exposed in early childhood to high levels of arsenic through the drinking-water. The temporal pattern of lung cancer mortality rate ratios in Region II compared with that in Region V (a low-exposure area) from 1950 to 2000, showed an increase about 10 years after the onset of high arsenic exposure, and peaked in 1986–87, with relative risks of 3.61 (95%CI: 3.13–4.16) and 3.26 (95%CI: 2.50–4.23) for men and women, respectively (Marshall *et al.*, 2007).

(b) Case–control and cohort studies

In northern Chile, a case–control study of 151 cases and 419 controls reported significantly increasing risks with increasing levels of arsenic during the 1958–70 high-exposure period, with an odds ratio increasing to 7.1 (95%CI: 3.4–14.8) (Ferreccio *et al.*, 2000).

In a cohort from south-western Taiwan (China), Chen *et al.* (1986) observed a dose–response relationship between the duration of consumption of artesian well-water containing high levels of arsenic and lung cancer mortality risk, showing the highest age- and gender-adjusted odds ratio among those who consumed artesian well-water for more than 40 years compared with those who never consumed artesian well-water. Another cohort study from south-western Taiwan (China) endemic for arsenic found a smoking-adjusted increased risk for lung cancer in relation to increasing average concentrations of arsenic and increasing cumulative exposure to arsenic (Chiou *et al.*, 1995).

A further study of combined cohorts in south-western (n = 2503) and north-eastern (n = 8088) Taiwan (China) found a synergistic interaction between arsenic in drinking-water and cigarette smoking (Chen *et al.*, 2004).

A case–control study from Bangladesh, conducted in 2003–06, found an elevated risk (odds ratio [OR], 1.65; 95%CI: 1.25–2.18) for male smokers consuming tube well-water with arsenic levels of 101–400 µg/L (Mostafa *et al.*, 2008). In non-smokers, the study did not report an increased risk with increasing arsenic exposure. [The Working Group noted the ecological nature of the exposure estimates, the possibility of greater sensitivity to arsenic exposure among smokers, and the relatively short latent period, with almost two-thirds of the wells put in place in 1990 or later.]

2.3 Cancer of the urinary bladder and of the kidney

The results of the epidemiological studies on arsenic in drinking-water and the risk for cancers of the urinary bladder and of the kidney are summarized in Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.7.pdf.

2.3.1 Ecological studies

In south-western and north-eastern Taiwan (China), the relation between cancer of the urinary bladder and of the kidney and drinking-water containing arsenic was evaluated in many of the studies cited above (Chen *et al.*, 1985, 1988a; Wu *et al.*, 1989; Chen & Wang, 1990; Tsai *et al.*, 1999). Each reported an elevation in mortality from these cancers during various time periods in 1971–94 associated with levels of arsenic in well-water from rural artesian wells, with many reporting a dose–response relationship among both men and women. An additional study, based on incidence records, found comparable risks for bladder cancer (Chiang *et al.*, 1993).

In Region II of Chile, two studies found markedly high SMRs for cancer of the urinary bladder and of the kidney in 1950–92 (Rivara *et al.*, 1997) and in 1989–93 (Smith *et al.*, 1998). In the latter study, mortality from chronic obstructive pulmonary disease was at the expected level, suggesting that smoking was not involved. The temporal pattern of bladder cancer mortality in Region II from 1950–2000 was compared with that in Region V (Marshall *et al.*, 2007). Increased relative risks were reported about 10 years after the start of exposure to high arsenic levels, with peak relative risks of 6.10 (95%CI: 3.97–9.39) for men, and 13.8 (95%CI: 7.74–24.5) for women in the period 1986–94. In Cordoba Province, Argentina, positive trends in SMRs were reported for bladder and kidney cancers associated with estimates of exposure to arsenic in drinking-water (Hopenhayn-Rich *et al.*, 1996, 1998), again with no findings for chronic obstructive pulmonary disease.

[The Working Group noted that kidney cancers consist of both renal cell carcinoma and transitional cell carcinoma of the renal pelvis, the latter often being of the same etiology as bladder cancer. As arsenic causes transitional cell carcinoma of the bladder, merging of the two types of kidney cancer may result in a dilution of the risk estimate for total kidney cancer.]

2.3.2 Case–control and cohort studies

In a case–control study using death certificates (1980–82) from the area in Taiwan (China), endemic for Blackfoot disease, Chen *et al.* (1986) reported increasing trends in odds ratios with increasing duration of consumption of artesian well-water containing arsenic. The highest risks were seen for over 40 years of exposure, with an odds ratio of 4.1 ($P < 0.01$) for bladder cancer in a multivariate analysis, after adjusting for smoking and other factors from next-of-kin interviews.

In case–control studies of incident bladder cancer that included analysis of arsenic species in urine samples, a higher risk associated with arsenic was found among persons with higher MMA^V:DMA^V ratios or, alternatively, with a higher percentage of MMA^V (Chen *et al.*, 2003, 2005a; Steinmaus *et al.*, 2006; Pu *et al.*, 2007a; Huang *et al.*, 2008).

Cohort studies from south-western and north-eastern Taiwan (China) (Chen *et al.*, 1988b; Chiou *et al.*, 1995, 2001; Chen & Chiou, 2001) Japan (Tsuda *et al.*, 1995), and the United Kingdom (Cuzick *et al.*, 1992) each observed elevated bladder cancer risk following long-term exposure to ingested arsenic, with dose–response relationships found where the numbers of cases permitted such an analysis. The study from Taiwan (China), also found an elevated risk of kidney cancer (OR, 2.8; 95%CI: 1.3–5.4, based on nine cases) (Chiou *et al.*, 2001).

2.4 Cancer of the skin

The recognition of arsenic as a carcinogen first came from case series describing skin cancers following the ingestion of medicines containing arsenicals (Hutchinson, 1888; Neubauer, 1947), and exposure to arsenical pesticide residues, and arsenic-contaminated wine (Roth, 1957; Grobe,

1977) or drinking-water, originating from many countries. The characteristic arsenic-associated skin tumours include squamous cell carcinomas arising in keratoses (including Bowen disease), and multiple basal cell carcinomas.

Findings of epidemiological studies on arsenic in drinking-water and risk for skin cancer are summarized in Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.8.pdf.

2.4.1 Ecological studies of prevalence

In south-western Taiwan (China), Tseng *et al.* (1968) found an 8-fold difference in the prevalence of skin cancer lesions from the highest (> 600 µg/L) to the lowest category (< 300 µg/L) of arsenic concentration in artesian wells, after an extensive examination survey of 40421 inhabitants in 37 villages.

2.4.2 Ecological studies based on mortality from cancer of the skin

Studies in Taiwan (China) (Chen *et al.*, 1985, 1988a; Wu *et al.*, 1989; Chen & Wang, 1990; Tsai *et al.*, 1999) analysed skin cancer mortality in relation to levels of arsenic in well-water. These investigations found consistent gradients of increasing risk with average level of arsenic in drinking-water, as measured on the township or precinct level.

Rivara *et al.* (1997) observed an SMR for skin cancer of 3.2 (95%CI: 2.1–4.8), comparing mortality from skin cancer in 1976–92 between Region II and the unexposed control Region VIII of Chile. Later, Smith *et al.* (1998) found SMRs of 7.7 (95%CI: 4.7–11.9) among men and 3.2 (95%CI: 1.3–6.6) among women for the years 1989–93 in Region II of Chile, using national mortality rates as reference. [The Working Group noted that the histological type of skin cancer was reported in only a few instances. Although skin cancer mortality can be influenced by access to health care, the SMRs reported here are so large as to not be explained by any possible confounding.]

2.4.3 Cohort studies

A retrospective cohort study of 789 (437 men, 352 women) of Blackfoot disease patients in Taiwan (China) reported an SMR of 28 (95%CI: 11–59) for skin cancer deaths (based on seven observed deaths), using Taiwan (China) regional rates as reference (Chen *et al.*, 1988b).

In a cohort of 654 persons in south-western Taiwan (China), an observed incidence rate of 14.7 cases of skin cancer/1000 person–years was found (Hsueh *et al.*, 1997), with risks significantly related to duration of living in the area endemic for Blackfoot disease, duration of consumption of artesian well-water, average concentration of arsenic, and index for cumulative exposure to arsenic. Similar findings were observed in a nested case–control study conducted within this cohort (Hsueh *et al.*, 1995).

In Region II of Chile, a decrease in incidence rates of cutaneous lesions (leukoderma, melanoderma, hyperkeratosis, and squamous cell carcinoma) was observed during 1968–71 after a lowering of waterborne arsenic levels from a filter plant, which started operation in 1970 (Zaldívar, 1974).

2.5 Cancer of the liver

2.5.1 Ecological studies

The relation between liver cancer risk and drinking-water contaminated with arsenic was evaluated in many of the studies from south-western Taiwan (China), cited above (Chen *et al.*, 1985, 1988a; Wu *et al.*, 1989; Chen & Wang, 1990; Chiang *et al.*, 1993; Tsai *et al.*, 1999; see Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.9.pdf), with positive associations found in all studies.

In northern Chile, Rivara *et al.* (1997) observed a relative risk for liver cancer mortality of 1.2 (95%CI: 0.99–1.6) in arsenic-exposed Region II compared with Region VIII. Liver cancer mortality in Region II of northern Chile during the period 1989–93 among persons ≥ 30 years of age was not significantly elevated, using national rates as reference (Smith *et al.*, 1998). SMRs were 1.1 (95%CI: 0.8–1.5) both for men and for women. Liaw *et al.* (2008) found an elevated relative risk (10.6; 95%CI: 2.9–39.3, $P < 0.001$) for liver cancer among children in Region II of Chile born in 1950–57 and exposed *in utero* or shortly thereafter, compared to rates in Region V of Chile.

In Cordoba Province, Argentina, SMRs were not related to arsenic exposure (Hopenhayn-Rich *et al.*, 1998).

[The Working Group noted that the finding of an association with liver cancer in Taiwan (China), but not in South America may reflect a more sensitive population in the former region, due to endemic hepatitis B. The elevated risk of those exposed *in utero* and as young children may reflect a combination of greater biological vulnerability in early life (Waalkes *et al.*, 2007) plus the fact that young children consume 5–7 times more water per kilogram body weight per day than adults (NRC, 1993).]

2.5.2 Case–control studies

In a case–control study investigating the consumption artesian well-water containing high concentrations of arsenic and mortality from liver cancer in four townships of south-westernern Taiwan (China), Chen *et al.* (1986) observed an exposure–response relationship between the duration of consumption of the contaminated well-water and risk for liver cancer, adjusted for cigarette smoking, habitual alcohol and tea drinking, and consumption of vegetables and fermented beans.

2.6 Cancer of the prostate

Studies conducted in Taiwan (China) (Chen *et al.*, 1985, 1988a; Wu *et al.*, 1989; Chen & Wang, 1990; Tsai *et al.*, 1999) analysed prostate cancer mortality in relation to levels of arsenic in well-water, with some overlap among the respective study populations. Using several methodological approaches and comparison populations including direct and indirect standardization of rates, all studies reported significant dose–response relationships between the level of arsenic in drinking-water and the risk for prostate cancer mortality (see Table 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.10.pdf).

In Chile, Rivara *et al.* (1997) found a relative risk of 0.9 (95%CI: 0.54–1.53) for prostate cancer, comparing the 1990 mortality rate for prostate cancer of Region II with that of Region VIII.

2.7 Synthesis

The Working Group reviewed a large body of evidence that covers ecological studies, case–control studies and cohort studies in a variety of settings and populations exposed either by ingestion (primarily to As^{III} and As^{V} in drinking-water) or inhalation (with exposure to a mixture of inorganic arsenic compounds). The evidence also relates to historical exposure from pesticidal and pharmaceutical uses. The epidemiological evidence from drinking-water exposure permits the evaluation of the carcinogenicity that is related to exposure to As^{III} and As^{V}. The epidemiological evidence from inhaled arsenic mixtures permits the evaluation of the carcinogenicity that is related to inorganic arsenic compounds. However, it does not allow a separation of the carcinogenic risk associated with particular arsenic species that occur in these mixtures.

The observed associations between exposure to arsenic in drinking-water and lung cancer, and between exposure to arsenic in air and lung

cancer, cannot be attributed to chance or bias. The evidence is compelling for both the inhalation and ingestion routes of exposure. There is evidence of dose–response relationships within exposed populations with both types of exposure.

The observed association between exposure to arsenic in drinking-water and bladder cancer cannot be attributed to chance or bias. There is evidence of dose–response relationships within exposed populations.

The observed association between exposure to arsenic in drinking-water and skin cancer cannot be attributed to chance or bias. There is evidence of dose–response relationships within exposed populations. The evidence is primarily for squamous cell carcinoma of the skin.

Although the data for kidney cancer are suggestive of a relationship with exposure to arsenic in drinking-water, overall, the small possibility of chance or bias cannot be completely ruled out.

The evidence for an association between liver cancer and long-term exposure to arsenic in drinking-water relies on mortality data. Although the data strongly suggest a causal association with some evidence of a dose–response relationship, the Working Group could not rule out possible chance or bias. The evidence comes mainly from Taiwan (China) where hepatitis B is highly prevalent.

The evidence for an association for prostate cancer and long-term exposure to arsenic in drinking-water relies on mortality data. In the studies from Taiwan (China), there is some evidence of a dose–response relationship. However, the data from South America are not consistent with this observation. Although the evidence on prostate cancer suggests the possibility of a causal association, the Working Group could not rule out the possibility of chance or bias.

3. Cancer in Experimental Animals

Over the years, it has proved difficult to provide evidence for the carcinogenesis of inorganic arsenic compounds. More recent work has focused on methylated arsenic metabolites in humans or exposure to inorganic arsenic during early life, and has provided the information to show potential links between arsenic and carcinogenesis.

Studies published since the previous *IARC Monograph* (IARC, 2004) are summarized below.

3.1 Oral administration

3.1.1 Mouse

The oral administration of sodium arsenate in drinking-water for 18 months increased lung tumour multiplicity and lung tumour size in male strain A/J mice (Cui *et al.*, 2006; see Table 3.1).

Similarly, drinking-water exposure to the organo-arsenical DMA^V for 50 weeks or more increased the incidence and multiplicity of lung adenoma or carcinoma in strain A/J mice (Hayashi *et al.*, 1998), and increased lung tumours in mutant *Ogg*–/– mice (which cannot repair certain types of oxidative DNA damage) but not in *Ogg*+/+ mice (Kinoshita *et al.*, 2007; see Table 3.2).

3.1.2 Rat

In male F344 rats, the oral administration of DMA^V in drinking-water for up to 2 years produced clear dose–response relationships for the induction of urinary bladder transitional cell carcinoma and combined papilloma or carcinoma (Wei *et al.*, 1999, 2002).

When DMA^V was added to the feed of male and female F344 rats for 2 years, a clear dose–response relationship for urinary bladder benign and/or malignant transitional cell tumours

Table 3.1 Studies of cancer in experimental animals exposed to sodium arsenate (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, A/J (M) 18 mo Cui *et al.* (2006)	0, 1, 10, 100 ppm arsenate in drinking-water, *ad libitum* 30/group	Lung (adenomas): 0/19, 0/13, 0/15, 4/30 (13%)	[NS, (any dose)][a]	Age at start, 5 wk Purity, NR Redundant Student *t*-test used for multiple comparisons of lung tumour multiplicity and size Survival significantly increased at high dose Non-dose-related, modest changes in bw, lung weight, and lung bw ratio
		Lung (adenocarcinomas): 9/19 (47%), 10/13 (77%), 11/15 (73%), 19/30 (63%)	[NS, (any dose)][a]	
		Average tumours/mouse lung: 0.59, 1.1, 1.3, 1.4[b]	$P < 0.01$ (all doses)	
		Average number tumours > 4 mm/mouse lung: 17, 32, 44, 60[b]	$P < 0.01$ (all doses)	

[a] Performed during review. One-sided Fisher Exact test–control versus all treated.
[b] Numbers are estimates at review because data are presented graphically in original work.
bw, body weight; M, male; mo, month or months; NR, not reported; NS, not significant; wk, week or weeks

occurred in female but not male rats (Arnold *et al.*, 2006). Preneoplasia (urothelial cell hyperplasia) was clearly increased in female rats (Arnold *et al.*, 2006; see Table 3.2).

In male F344 rats, the oral administration of trimethylarsine oxide in drinking-water for 2 years caused a significant increase of benign liver tumours (adenoma) (Shen *et al.*, 2007; see Table 3.3).

Oral exposure to MMA^V for 2 years was negative in a comprehensive dose–response study including male and female rats and mice, although body weight suppression and reduced survival with the higher doses confounded the rat segment of the study (Arnold *et al.*, 2003; see Table 3.4).

A 2-year dose–response study with sodium arsenite showed some evidence of renal tumour formation in female Sprague-Dawley rats but not in males (Soffritti *et al.*, 2006). Tumour incidence did not reach significance (see Table 3.5).

3.2 Intratracheal administration

3.2.1 Hamster

Repeated weekly intratracheal instillations of calcium arsenate, at levels sufficient to caused moderate early mortality, increased lung adenoma formation in male Syrian golden hamsters when observed over their lifespan (Pershagen & Björklund, 1985).

In a similarly designed study, male hamsters received multiple weekly intratracheal instillations of calcium arsenate at the start of the experiment, and developed an increased incidence of lung adenoma formation, and combined lung adenoma or carcinoma formation over their lifespan (Yamamoto *et al.*, 1987; see Table 3.6).

Intratracheal instillations of calcium arsenite increased the incidence of respiratory tract carcinoma and combined adenoma, papilloma and adenomatoid lesion formation in male Syrian Hamsters (Pershagen *et al.*, 1984; see Table 3.7).

Table 3.2 Studies of cancer in experimental animals exposed to dimethylarsinic acid, DMA^V (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, A/J (M) 50 wk Hayashi *et al.* (1998)	0, 50, 200, 400 ppm DMA^V in drinking-water, *ad libitum* 24/group	Number of mice with lung papillary adenomas or adenocarcinomas: 2/14 (14%), 5/14 (36%), 7/14 (50%), 10/13 (77%)	$P < 0.01$ (high dose)	Age at start, 5 wk Purity, NR Survival unremarkable [Only histologically confirmed tumours were considered by the Working Group]
Mouse, *Ogg1-/-* and *Ogg1+/+* (M, F) 72 wk Kinoshita *et al.* (2007)	0, 200 ppm DMA^V in drinking-water, *ad libitum*; controls received tap water 10/group (*Ogg1-/-*) 12/group (*Ogg1+/+*)	***Ogg1-/-:*** Tumour-bearing mice (any site): 0/10, 10/10 (100%)	$P < 0.01$	Age at start, 14 wk Purity, 99% Bw and food and water consumption unremarkable Left lobe and visible lung nodules used for histopathological tumour analysis Treated *Ogg1–/–* showed modest decreased survival (~20%) late compared to phenotypic control Small groups
		Lung lesions– Hyperplasias: 10/10 (100%), 10/10 (100%)		
		Adenomas: 0/10, 2/10 (20%)	NS	
		Adenocarcinomas: 0/10, 3/10 (30%)		
		Total lung tumours: 0/10, 5/10 (50%)	$P < 0.05$	
		Tumours/mouse: 0, 0.5	$P < 0.05$	
		Ogg1+/+: Tumour-bearing mice (any site): 5/10 (50%), 6/10 (60%)		
		Lung lesions– Hyperplasias: 2/10 (20%), 10/10 (100%)	[$P < 0.01^b$]	
		Adenomas: 1/10 (10%), 0/10	NS	
		Adenocarcinomas: 0/10, 0/10	NS	
		Total tumours: 1/10 (10%), 0/10	NS	
		Tumours/mouse: 0.1, 0	NS	
		Tumours/mouse: 0.1, 0	NS	

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M) 104 wk Wei *et al.* (1999)[d], 2002)	0, 12.5, 50, 200 ppm DMA^{V} in drinking-water, *ad libitum* 36/group	Urinary bladder (hyperplasias): 0/28, 0/33, 12/31 (39%), 14/31 (45%) Urinary bladder (papillomas): 0/28, 0/33, 2/31 (2%), 2/31 (2%) Urinary bladder (carcinomas): 0/28, 0/33, 6/31 (19%), 12/31 (39%) Urinary bladder (papillomas or carcinomas): 0/28, 0/33, 8/31 (26%), 12/31 (39%)	$P < 0.01$ (middle and high dose) NS $P < 0.05$ (middle dose) $P < 0.01$ (high dose) $P < 0.01$ (middle and high dose)	Age at start, 10 wk Purity, 99% Survival and food intake unaltered Transient bw suppression early with high and middle dose but then similar to control Water intake increased at highest two doses Incidence rates based on rats at risk (surviving to time of the first bladder tumour at 97 wk) Extensive necropsy
Rat, F344 (M, F) 104 wk Arnold *et al.* (2006)	0, 2, 10, 40, 100 ppm DMA^{V} in feed, *ad libitum* 60/group	**Females** Urothelial cell (hyperplasias, simple, nodular and papillary): 0/60, 1/59 (2%), 0/60, 29/59 (49%), 48/60 (80%) Urinary bladder (papillomas): 0/60, 0/59, 0/60, 0/59, 4/60 (7%) Urinary bladder (carcinomas): 0/60, 0/59, 0/60, 0/59, 6/60 (10%) Urinary bladder (papillomas and carcinomas combined): 0/60, 0/59, 0/60, 0/59, 10/60 (3%) **Males** Urothelial cell (hyperplasias, simple, nodular and papillary): 0/60, 0/59, 0/60, 6/58 (10%), 40/59 (68%) Urinary bladder (papillomas): 0/60, 0/59, 1/60 (2%), 1/58 (2%), 0/59 Urinary bladder (carcinomas): 0/60, 1/59 (2%), 0/60, 0/58, 2/59 (3%) Urinary bladder (papillomas and carcinomas combined): 0/60, 1/59 (2%), 1/60 (2%), 1/58 (2%), 2/59 (3%)	$P < 0.01$ (trend) [$P < 0.01$ (highest, and second highest dose)][b] [NS (high dose)][b] $P < 0.01$ (trend)[c] [$P < 0.05$ (high dose)][b] $P < 0.01$ (trend)[c] [$P < 0.05$ (high dose)][b] $P < 0.01$ (trend) [$P < 0.01$ (high dose)][b] [NS (high dose)][b] $P < 0.01$ (trend)[c] [NS (high dose)][b] $P < 0.01$ (trend)[c] [NS (high dose)][b]	Purity > 99%; age, 5 wk Complete necropsies performed No treatment-related differences in mortality or bw Sporadic changes in food consumption not treatment-related Water consumption increased with treatment Water consumption increased with treatment

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F1 (F) 104 wk Arnold *et al.* (2006)	0, 8, 40, 200, 500 ppm DMA^V in feed, *ad libitum* 56/group	**Females** No treatment-related changes in urinary bladder preneoplasia or tumour incidence noted		Age at start, 5 wk Purity 99% Complete necropsies performed Survival, bw and water consumption unchanged Sporadic, small changes in food consumption early Fibrosarcomas not considered related to treatment by authors Bw reduced at 500 ppm throughout study
		Any organ (fibrosarcomas): 3/56 (5%), 0/55, 1/56 (2%), 1/56 (2%), 6/56 (11%)	$P < 0.01$ (high dose)	
		Males No treatment-related changes in urinary bladder preneoplasia or tumour incidence noted		

[a] Data also included descriptive statistics (i.e. SD).
[b] Performed during review. One-sided Fisher exact test control versus treated.
[c] Trend analysis performed after combination of female and male data for urinary bladder lesions from this same study (Arnold *et al.*, 2006).
[d] Short communication of tumour data only.
[e] On a C57BL/6 background.
[f] As stated by the authors.
[g] The lack of information on group size and the lack of descriptive statistics makes these data impossible to independently re-evaluate for statistical significance.
bw, body weight; F, female; M, male; NR, not reported; NS, not significant; wk, week or weeks

Table 3.3 Studies of cancer in experimental animals exposed to trimethylarsine oxide (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M) 2 yr Shen *et al.* (2003)	0, 50, 200 ppm trimethylarsine oxide in drinking-water, *ad libitum* 42–45; 42 controls	Liver (adenomas): 6/42 (9%), 10/42 (14%), 16/45 (24%)	$P < 0.05$ (high dose)	Age at start, 10 wk Purity, 99% Body weights, food intake, water intake, survival rate, and average survival unaltered with treatment Extensive necropsy performed Various other sites negative

bw, body weight; M, male; yr, year or years

3.3 Intravenous administration

3.3.1 Mouse

Multiple intravenous injections of sodium arsenate in male and female Swiss mice provided no evidence of elevated tumour formation (Waalkes *et al.*, 2000; see Table 3.8).

3.4 Transplacental and perinatal exposures

3.4.1 Mouse

Pregnant mice were treated subcutaneously with arsenic trioxide on a single specific day during gestation (Days 14, 15, 16 or 17), and the offspring were then treated subcutaneously on *postpartum* Days 1, 2 and 3 with arsenic trioxide. The offspring initially treated on Day 15 of gestation developed an excess of lung adenoma compared to controls, and the other groups did not (Rudnai & Borzsanyi, 1980, 1981; see Table 3.9).

Pregnant C3H mice were exposed to various doses of sodium arsenite in the drinking-water from Days 8–18 of gestation. They were allowed to give birth and their offspring were put into gender-based groups at weaning. Over the next 90 weeks, arsenic-treated female offspring developed dose-related benign and/or malignant ovarian tumours, and lung adenocarcinoma. During the next 74 weeks, a dose-related increase in the incidences of liver adenoma and/or carcinoma, and adrenal cortical adenoma was observed in the male offspring (Waalkes *et al.*, 2003).

A second study looked at the carcinogenic effects in C3H mice of various doses of sodium arsenite (two levels) in the maternal drinking-water from Days 8 to 18 of gestation, with or without subsequent 12-*O*-tetradecanoyl phorbol-13-acetate (TPA) applied to the skin of the offspring after weaning from 4–25 weeks of age. Over the next 2 years, with arsenic alone, the female offspring developed an increased incidence of ovarian tumours. The male offspring developed arsenic dose-related increases in the incidences of liver adenoma and/or carcinoma and adrenal cortical adenoma (Waalkes *et al.*, 2004).

Pregnant CD1 mice received sodium arsenite (one level) in the drinking-water from gestation Days 8 to 18, were allowed to give birth, and the female (Waalkes *et al.*, 2006a) or male (Waalkes *et al.*, 2006b) offspring were treated with diethylstilbestrol or tamoxifen subcutaneously on *postpartum* Days 1, 2, 3, 4 and 5. In female offspring over the next 90 weeks, arsenic exposure alone

Table 3.4 Studies of cancer in experimental animals exposed to monomethylarsonic acid, MMA^V (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F1 (M, F) 104 wk Arnold *et al.* (2003)	0, 10, 50, 200, 400 ppm MMA^V in feed, *ad libitum* 52/group/sex	No treatment-related changes		Age at start, 6 wk Purity, 99% Bw reduced at 400 ppm throughout study Food and water consumption similar or increased at the two higher doses Survival unremarkable Complete necropsy performed
Rat, F344 (M, F) 104 wk Arnold *et al.* (2003)	0, 50, 400, 1 300[a] ppm MMA^V in feed, *ad libitum* 60/group/sex	No treatment-related changes		Age at start, 6 wk Purity, 99% Bw reduced at two highest doses in second half of study Food consumption generally similar Water consumption similar or increased at the two higher doses Survival reduced at high dose Complete necropsy performed

[a] Due to a high mortality in male and female rats fed this level, it was reduced to 1000 ppm during Week 53, and further reduced to 800 ppm during Week 60.
bw, body weight; F, female; M, male; wk, week or weeks

Table 3.5 Studies of cancer in experimental animals exposed to sodium arsenite (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley (M, F) 167 wk (lifespan) Soffritti *et al.* (2006)	0, 50, 100, 200 mg/L $NaAsO_2$ in drinking-water, *ad libitum* from onset to 104 wk 50/group	Kidney (tumours): F– 1/50 (2%), 1/50 (2%), 5/50 (10%), 5/50 (10%)[c] M– 0/50, 2/50 (4%), 2/50 (4%), 0/50	NS for both sexes	Age at start, 8 wk Purity 98% Complete necropsy performed Reduced water and food intake especially at two highest doses Dose-related reduced bw

[a] As stated by the authors.
[b] The lack of information on group size and lack of descriptive statistics makes the data from this work impossible to re-evaluate for statistical significance.
[c] Includes three carcinomas at the high dose and one at the second highest dose in females and a carcinoma in females at the second highest dose.
Bw, body weight; F, female; M, male; NS, not significant; wk, week or weeks

increased the incidence of tumours of the ovary, uterus, and adrenal cortex. In the male offspring, prenatal arsenic exposure alone increased liver adenoma and/or carcinoma, lung adenocarcinoma, and adrenal cortical adenoma (see Table 3.10).

3.5 Studies in which arsenic modifies the effects of other agents

3.5.1 Mouse

Mice exposed to DMA^V in drinking-water after subcutaneous injection of 4-nitroquinoline 1-oxide showed an increase in lung tumour multiplicity compared to mice exposed to the organic carcinogen alone (Yamanaka *et al.*, 1996). In K6/ODC mice first treated topically with 7,12-dimethylbenz[α]anthracene (DMBA) then with DMA^V in a cream applied to the same skin area for 18 weeks, the organo-arsenical doubled the skin tumour multiplicity compared to treatment with DMBA alone (Morikawa *et al.*, 2000; see Table 3.11). [The Working Group noted that this study had too few DMA^V controls for an appropriate interpretation.]

In the studies of Germolec *et al.* (1997, 1998), oral sodium arsenite was given to Tg.AC mice with TPA by skin painting, and an approximately 4-fold increase in skin tumour response was reported.

Combined treatment with oral sodium arsenite in drinking-water and multiple exposures to excess topical UV irradiation in Crl:SKl-*hr*BR hairless mice showed that arsenic treatment alone was consistently without carcinogenic effect, but markedly enhanced UV-induced skin tumours including squamous cell carcinoma (Rossman *et al.*, 2001; Burns *et al.*, 2004; Uddin *et al.*, 2005). In another skin study, mice exposed to topical 9,10-dimethyl-1,2-benzanthracene for 2 weeks concurrently with oral sodium arsenate in drinking-water for 25 weeks showed that arsenic treatment alone was without carcinogenic effect, but enhanced skin tumour multiplicity and tumour size when combined with the organic carcinogen compared to the organic carcinogen alone (Motiwale *et al.*, 2005; see Table 3.12).

When pregnant Tg.AC mice were treated with oral sodium arsenite in drinking-water from Days 8–18 of gestation, and their offspring were topically exposed to TPA from 4–40 weeks

Table 3.6 Studies of cancer in experimental animals exposed to calcium arsenate (intratracheal instillation)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Hamster, Syrian golden (M) ~145 wk (lifespan) Pershagen & Björklund (1985)	0, ~3 mg As/kg bw in 0.15 mL saline once/wk for 15 wk 41; 29 controls	Lung (adenomas): 0/26, 4/35 (11%)	$P < 0.05$	Age at start, 8 wk Purity, ultrapure Mortality during dosing ~15%; mortality increased in arsenate group during second yr Dose approximate
Hamster, Syrian golden (M) Up to 115 wk in treated animals, and 121 wk in controls (lifespan) Yamamoto *et al.* (1987)	0, 0.25 mg As in 0.1 mL saline once/wk for 15 wk 30; 22 controls	Lung (adenomas): 0/22, 6/25 (24%) Lung (carcinomas): 1/22 (4%), 1/25 (4%) Lung (adenomas and carcinomas combined): 1/22 (4%), 7/25 (3%)	[$P < 0.01$[a]] NS *P*-value not reported but stated as significant [$P < 0.01$[a]]	Age at start, 8 wk Purity, chemical grade Instillations caused 10% mortality and reduced survival ~10% post-instillation Bw not recorded during experiment

[a] Calculated by the Working Group. One-sided Fisher exact test control versus treated.
bw, body weight; M, male; NS, not significant; wk, week or weeks

Table 3.7 Studies of cancer in experimental animals exposed to arsenic trioxide (intratracheal instillation)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Hamster, Syrian golden (M) Up to ~140 wk (lifespan) Pershagen *et al.* (1984)[a]	0 or ~3 mg As/kg bw in 0.15 mL saline once/wk for 15 wk 67; 68 controls	Larynx, trachea, bronchus, or lung (carcinomas): 0/53, 3/47 (6%) Larynx, trachea, bronchus, or lung (adenomas, adenomatoid lesions, and papillomas combined): 7/53 (13%), 24/47 (51%)	NS [$P < 0.01$]	Age at start, 7–9 wk Purity, 99.5% Doses approximate Instillation mixture for arsenic contained carbon dust and 2 mM sulfuric acid (not in controls) Significant mortality during dosing (29%) “Adenomatoid lesion” not defined, presumably focal hyperplasia

[a] Arsenic trioxide was also given with benzo[*a*]pyrene and the combination appeared to increase combined adenoma, adenocarcinoma and adenosquamous carcinoma in the bronchi and lungs compared to benzo[*a*]pyrene alone but the data are listed (total tumours/group and not incidence) such that this cannot be independently confirmed.
bw, body weight; M, male; NS, not significant; wk, week or weeks

Table 3.8 Studies of cancer in experimental animals exposed to sodium arsenate (intravenous exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Swiss CR:NIH(S) (M, F) 96 wk Waalkes *et al.* (2000)	0, 0.5 mg As/kg bw in 10 mL/kg in saline once/wk for 20 wk staring at onset; controls received saline[a] 25/group/sex	**M** Lymphomas: 1/25 (4%), 1/25 (4%)	NS	Age at start, 8 wk Purity, NR Survival and bw not remarkable No leukaemias were observed
		Testicular interstitial cell hyperplasias: 8/25 (32%), 16/25 (64%)	$P < 0.05$	
		Skin hyperkeratosis: 1/25 (4%), 5/25 (20%)	NS	
		F Lymphomas: 5/25 (20%), 3/25 (12%)	NS	
		Uterine cystic hyperplasias: 5/25 (20%), 14/25 (56%)[b]	$P < 0.05$	

[a] Based on the treatment regimen ofOsswald & Goerttler (1971).
[b] A uterine adenocarcinoma was also observed with arsenate treatment that is noteworthy because of its spontaneous rarity in historical controls of this strain.
bw, body weight; F, female; M, male; NR, not reported; NS, not significant; wk, week or weeks

Table 3.9 Studies of cancer in experimental animals exposed to arsenic trioxide (perinatal exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, CFLP (NR) 1 yr Rudnai & Borzsanyi (1980), Rudnai & Borzsanyi (1981)[a]	Single dose of 1.2 mg/kg arsenic trioxide bw s.c. at gestation Day 14, 15, 16, or 17 Test offspring: 5 µg arsenic trioxide/mouse s.c. postpartum Day 1, 2 and 3 Controls untreated Offspring group sizes at start (NR)	Lung (adenomas and adenocarcinomas):[b] Control–3/17 (17%) Day 14–14/36 (39%) Day 15–12/19 (63%) Day 16–3/20 (15%) Day 17–6/20 (30%)	$P < 0.01$ (Day 15)[b]	Purity stated as “purum” Pregnancy verified by smear and when positive designated Day 0 Dam number used to derive offspring groups NR Lung and gross lesions histologically examined Survival and bw NR Gender NR and probably mixed Numbers of specific lung tumours NR

[a] In Hungarian. Tumour incidence data are numerically the same for this and theRudnai & Borzsanyi (1980) manuscript, but vary in that the treatment day of pregnancy which lead to a significant increase in lung adenoma in the first paper (Day 15) shifted to one day later in the second paper (Day 16). Communication with the primary author revealed that this discrepancy in the re-reporting (Rudnai & Borzsanyi, 1981) is due to a difference in calling the first day on which pregnancy was indicated Day 1 of gestation rather than Day 0 as in the original report (Rudnai & Borzsanyi, 1980). Thus, the treatment regimen and data from the primary paper are herein reported.

[b] The gestational treatment day is given in parentheses before incidence or after indication of significance.

bw, body weight; NR, not reported; s.c., subcutaneously; yr, year or years

Table 3.10 Studies of cancer in experimental animals exposed to sodium arsenite (transplacental exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, C3H/HeNCr (M, F) 90 wk (*postpartum*) for F 74 wk (*postpartum*) for M Waalkes *et al.* (2003)	Maternal exposure: 0, 42.5, 85 ppm As in drinking-water, *ad libitum* from gestation Day 8–18 Offspring; 25/group/sex	**Females** Ovary (tumours): Benign–2/25 (8%), 4/23 (17%), 8/24 (33%)	$P < 0.05$ (high dose plus trend)	Purity,[a] NR 10 Pregnant mice used to derive each group of offspring Offspring weaned at 4 wk Maternal water consumption and bw unaltered Offspring bw unaltered Survival in offspring unaltered in females Survival reduced at high dose in due to liver carcinoma in males
		Malignant–0/25, 2/23 (9%), 1/24 (4%)	NS	
		Benign or malignant combined– 2/25 (8%), 6/23 (26%), 9/24 (37%)	$P < 0.05$ (high dose) $P < 0.05$ (trend)	
		Lung (carcinomas): 0/25, 1/23 (4%), 5/24 (20%)	$P < 0.05$ (high dose) $P < 0.05$ (trend)	
		Males Liver (adenomas): 9/24 (37%), 9/21 (43%), 20/23 (87%)	$P < 0.01$ (high dose)	
		Liver (hepatocellular carcinomas): 2/24 (8%), 8/21 (38%), 14/23 (61%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Liver (adenomas or hepatocellular carcinomas): 10/24 (42%), 11/21 (52%), 20/23 (87%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Liver tumours/mouse: 0.87, 1.81, 4.91	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Adrenal cortex (adenomas): 9/24 (37%), 14/21 (67%), 21/23 (91%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Adrenal adenomas/mouse: 0.71, 1.10, 1.57	$P < 0.05$ (high dose) $P < 0.05$ (trend)	

Table 3.10 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, C3H/HeNCr (M, F) 104 wk (*postpartum*) Waalkes *et al.* (2004)	Maternal exposure: 0, 42.5, 85 ppm As in drinking-water, *ad libitum* from gestation Day 8–18 Offspring exposure: topical 2 µg[b] TPA/0.1 mL acetone, twice/wk from 4–25 wk of age applied to shaved back, controls received acetone Offspring groups: 25/group/sex	**Females** Liver (adenomas or hepatocellular carcinomas):		Purity,[a] NR 10 Pregnant mice used to derive each group of offspring Litters culled at 4 d *postpartum* to no more than 8 pups Maternal water consumption and bw unaltered Small bw reductions (~10%) occurred late (> 95 wk) in the high-dose (85 ppm) female offspring TPA did not alter bw Survival unaltered Inclusion of TPA did not have an impact on skin cancers
		Without TPA–3/24 (12%), 6/23 (26%), 4/21 (19%)	NS	
		With TPA–3/24 (12%), 6/22 (27%), 8/21 (38%)	$P < 0.05$ (high dose and trend)	
		Liver tumour multiplicity (tumours/mouse):		
		Without TPA–0.13, 0.41, 0.29	NS	
		With TPA–0.13, 0.32, 0.71	$P < 0.05$ (high dose and trend)	
		Ovary (tumours):[c]		
		Without TPA–0/24, 5/23 (22%), 4/21 (19%)	$P < 0.05$ (both doses)	
		With TPA–0/24, 5/22 (23%), 4/21 (19%)	$P < 0.05$ (both doses)	
		Lung (adenomas):		
		Without TPA–1/24 (4%), 2/23 (9%), 2/21 (9%)	NS	
		With TPA–1/24 (4%), 2/22 (9%), 6/21 (29%)	$P < 0.05$ (high dose and trend)	
		Males Liver (tumours):		Arsenic group not given TPA due to liver carcinoma (males)
		Adenomas without TPA–10/24 (42%), 12/23 (52%), 19/21 (90%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Adenomas with TPA–8/23 (35%), 12/23 (52%), 16/21 (76%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Hepatocellular carcinomas without TPA–3/24 (12%), 8/23 (35%), 10/21 (48%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Hepatocellular carcinomas with TPA–2/23 (9%), 6/23 (26%), 7/21 (33%)	$P < 0.05$ (high dose and trend)	
		Adenomas or hepatocellular carcinomas without TPA–12/24 (50%), 14/23 (52%), 19/21 (90%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	

Table 3.10 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Waalkes *et al.* (2004) (contd.)		Adenomas or hepatocellular carcinomas with TPA–9/23 (39%), 15/23 (65%), 18/21 (90%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Multiplicity without TPA: 0.75, 1.87, 2.14	$P < 0.05$ (both doses) $P < 0.01$ (trend)	
		Multiplicity with TPA: 0.61, 1.44, 2.14	$P < 0.05$ (both doses) $P < 0.01$ (trend)	
		Adrenal cortex (adenomas): Without TPA–9/24 (37%), 15/23 (65%), 15/21 (71%)	$P < 0.05$ (high dose and trend)	
		With TPA–7/23 (30%), 15/23 (65%), 12/21 (57%)	$P < 0.05$ (low dose)	
		Lung (adenomas): Without TPA–4/24 (17%), 6/23 (26%), 5/21 (24%)	NS	
		With TPA–2/23 (9%), 10/23 (43%), 5/21 (24%)	$P < 0.05$ (low dose)	
Mouse, CD1 (M, F) 90 wk (*postpartum*) Waalkes *et al.* (2006a, b)[k]	Maternal exposure: 0, 85 ppm As in drinking-water, *ad libitum* from gestation Day 8–18 Offspring exposure: *Postpartum* Day 1, 2, 3, 4, and 5 2 µg DES[d]/pup/d s.c., or 10 µg TAM[e]/pup/d s.c., or vehicle (corn oil; control) (control, As, DES, TAM, As + DES, As + TAM) 35/group/sex	**Females** Ovary (tumours):[h] 0/33, 7/34 (21%), 2/33 (6%), 1/35 (3%), 9/33 (26%), 5/35 (14%)	$P < 0.05$ (As, As + DES, As + TAM)	Purity 97.0% $NaAsO_2$ 12 Pregnant mice used to derive each group of offspring Litters culled after birth to no more than 8 pups Maternal water consumption unaltered Maternal and offspring bw unaltered
		Uterus (adenomas): 0/33, 3/34 (9%), 0/33, 0/35, 0/33, 0/35	NS	
		Uterus (carcinomas): 0/33, 2/34 (6%), 0/33, 2/35 (6%), 7/33 (21%), 2/35 (6%)	$P < 0.05$ (As + DES)	
		Uterus (adenomas or carcinomas): 0/33, 5/34 (15%), 0/33, 2/35 (6%), 7/33 (21%), 2/35 (6%)	$P < 0.05$ (As, As + DES)	
		Vagina (carcinomas): 0/33, 0/34, 1/33, 0/35, 5/33[g] (15%), 0/35	$P < 0.05$ (As + DES)	
		Adrenal cortex (adenomas): 1/33 (3%), 9/34 (26%), 3/33 (9%), 2/35 (6%), 8/33 (24%), 7/35 (20%)	$P < 0.05$ (As, As + DES, As + TAM)	
		Urinary bladder lesions:		

Table 3.10 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Waalkes *et al.* (2006a, b) (contd)		Hyperplasias– 1/33 (3%), 5/34 (15%), 1/33 (3%), 0/35, 10/33 (30%), 9/35 (26%)	$P < 0.05$ (As + DES, As + TAM)	
		Papillomas– 0/33, 0/34, 0/33, 0/35, 0/33, 1/35 (3%)	NS	
		Carcinomas[i]– 0/33, 0/34, 0/33, 0/35, 3/33 (9%), 0/35	NS	
		Total proliferative lesions[j]– 1/33 (3%), 5/34 (15%), 1/33 (3%), 0/35, 13/33[g] (38%), 10/35[g] (29%)	$P < 0.05$ (As + DES, As + TAM)	
		Liver (tumours any type): 0/33, 4/34 (12%), 1/33 (3%), 0/35, 5/33 (15%), 4/35 (11%)	$P < 0.05$ (As + DES)	
		Males Liver (tumours):		Purity sodium arsenite 97.0%; DES 99%, TAM 99% Bw transiently reduced (~15%) by DES or TAM early but recovery to control levels by 5–20 wk *postpartum* Survival unaltered by prenatal arsenic alone. Survival reduced in all other treatment groups (DES, TAM, As + DES, As + TAM) from ~20 wk on compared to control[l] (males)
		Adenomas– 2/35 (6%), 8/35 (23%), 1/33 (3%), 0/30, 12/29 (41%), 9/30 (30%)	$P < 0.05$ (As, As + DES, As + TAM)	
		Hepatocellular carcinomas– 0/35, 5/35 (14%), 0/33, 0/30, 4/29 (14%), 5/30 (17%)	$P < 0.05$ (As, As + DES, As + TAM)	
		Adenomas or carcinomas– 2/35 (6%), 11/35 (31%), 1/33 (3%), 0/30, 14/29 (48%), 14/30 (47%)	$P < 0.05$ (As, As + DES,)	
		Lung (adenocarcinomas): 2/35 (6%), 9/35 (26%), 2/33 (6%), 0/30, 4/29 (14%), 6/30 (20%)	$P < 0.05$ (As)	
		Adrenal cortex (adenomas): 0/35, 13/35 (37%), 0/33, 0/30, 9/29 (31%), 11/30 (37%)	$P < 0.05$ (As, As + DES, As + TAM)	
		Urinary bladder lesions: Hyperplasias– 0/35, 3/35 (9%), 4/33 (12%), 3/30 (10%), 13/29[g] (45%), 9/30[g] (30%)	$P < 0.05$ (As + DES, As + TAM)	
		Papillomas– 0/35, 0/35, 0/33, 0/30, 0/29, 3/30 (10%)	NS	

Table 3.10 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Waalkes *et al.* (2006a, b) (contd)		Carcinomas[i]– 0/35, 0/35, 0/33, 0/30, 1/29 (3%), 1/30 (3%)	NS	
		Papillomas or carcinomas– 0/35, 0/35, 0/33, 0/30, 1/29 (3%), 4/30[g] (13%)	$P < 0.05$ (As + TAM)	
		Total proliferative lesions[j]– 0/35, 3/35 (9%), 4/33 (12%), 3/30 (10%), 13/29[g] (45%), 14/30[g] (40%)	$P < 0.05$ (As + DES, As + TAM)	

[a] Purity given in Waalkes *et al.* (2006a) using same chemical source is 97.0%.
[b] 12-*O*-tetradecanoyl phorbol-13-acetate.
[c] Exclusively epithelial and primarily adenoma.
[d] Diethylstilbestrol
[e] Tamoxifen
[f] Included benign and malignant epithelial and mesenchymal tumours within components of the urogenital system (ovary, oviduct, uterus, cervix, vagina, kidney, and urinary bladder).
[g] Incidence for arsenic plus DES or arsenic plus TAM was significantly ($P < 0.05$) higher than arsenic alone.
[h] Primarily adenoma.
[i] Exclusively transitional cell carcinoma.
[j] Defined by the authors as the incidence of mice bearing at least one uroepithelial preneoplasia (hyperplasia), papilloma, or carcinoma.
[k] Run concurrently with and derived from the same mothers as the females in Waalkes *et al.* (2006a) study but reported separately.
[l] Reduced survival in these groups appeared dependent on moderate to extensive kidney damage due to DES and TAM in male mice and appeared unrelated to arsenic exposure.
[m] Two renal tumours also occurred in this group including, an adenoma and a renal cell carcinoma, against none in control, which are noteworthy because of their rare spontaneous occurrence in mice.
d, day or days; DES, diethylstilbestrol; F, female; M, male; NR, not reported; NS, not significant, s.c., subcutaneously; TAM, tamoxifen; wk, week or weeks

Table 3.11 Studies where arsenicals given after other agents enhance carcinogenesis while having no effect alone in experimental animals

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, ddy (M) 25 wk Yamanaka *et al.* (1996)	Initiation 10 mg 4NQO[e]/kg bw s.c. then 200 or 400 ppm DMA^V in drinking-water for 25 wk Groups: 4NQO alone, 4NQO + 200 ppm DMA, 4NQO + 400 ppm DMA 9–13/group	Macroscopic lung tumours/ mouse: 0.22, 3.92, 4.38	*P* < 0.05 (high dose)	Age at start, 6 wk DMA^V purity, NR Bw and survival unremarkable DMA^V alone group not included Lung only Microscopic analysis of lung tumours not reported (largely confirmed as tumours) Small group sizes
Mouse, *K6/ODC* (C57BL/6J background) 20 wk Morikawa *et al.* (2000)	Single 50 µg dose of DMBA[f]/mouse topical dorsal skin at Week 1; then 3.6 mg DMA^V/mouse in “neutral cream” to dorsal skin twice/wk, Week 2–19 Groups: DMBA, DMBA + DMA^V 7; 8 controls (DMBA)	Macroscopic skin tumours/ mouse: 9.7, 19.4	*P* < 0.05	Age at start, 10–14 wk DMA^V purity, NR Bw and survival unremarkable DMA^V-alone group had only 2 mice; skin tumours not reported Small group sizes Skin only No quantitative microscopic analysis of skin tumours
Rat, Wistar (M) 175 d Shirachi *et al.* (1983)	Sodium arsenite Partial heptectomy, 18–24 h later 30 mg DEN[a]/kg i.p.; 7 d later 160 ppm As in drinking-water Number at start, NR	Renal tumours: 0/10, 1/7 (14%), 0/9, 7/10 (70%)	*P* < 0.05	Age at start, NR Purity, NR Arsenic lowered bw and water intake Limited reporting and never reported in full

Table 3.11 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344/DuCrj (M) 30 wk Yamamoto *et al.* (1995)	Initial pretreatment with 5 known carcinogens (termed DMBDD[b]) then 0, 50, 100, 200, 400 ppm DMA^V in the drinking-water during Week 6–30 Groups: DMBDD alone, DMBDD + 50 ppm DMA^V, DMBDD + 100 ppm DMA^V, DMBDD + 200 ppm DMA^V, DMBDD + 400 ppm DMA^V 20/group	Urinary bladder:[c]		Age at start, 7 wk DMA^V purity, 99%; DMA^V initially lowered but then increased bw; changes moderate and at high dose DMA^V increased water intake at high dose Survival unremarkable Separate 100 and 400 ppm (12 each) DMA^V alone groups were included but had no tumours or preneoplastic lesions
		Papillomas– 1/20 (5%), 12/20 (60%), 12/19 (63%), 11/20 (55%), 7/20 (35%)	$P < 0.01$ (three lowest) $P < 0.05$ (highest)	
		Transitional cell carcinomas– 1/20 (5%), 10/20 (50%), 11/19 (60%), 12/20 (60%), 13/20 (65%)	$P < 0.01$ (all DMA^V treatment groups)	
		Papillomas or carcinomas– 2/20 (10%), 17/20 (85%), 16/19 (84%), 17/20 (85%), 16/20 (80%)	$P < 0.01$ (all DMA^V treatment groups)	
		Kidney:		
		Adenomas– 1/20 (5%), 3/20 (15%), 1/19 (5%), 7/20 (35%), 3/20 (15%)	$P < 0.01$ (second highest)	
		Adenocarcinomas– 0/20, 0/20, 2/19 (10%), 1/20 (5%), 7/20 (35%)	$P < 0.01$ (high dose and trend)	
		Total– 5/20 (25%), 3/20 (15%), 6/19 (30%), 13/20 (65%), 13/20 (65%)	$P < 0.05$ (trend)	
		Liver:		
		Hepatocellular carcinomas– 0/20, 2/20 (10%), 0/19, 8/20 (40%), 8/20 (40%)	$P < 0.05$ (highest two and trend)	
		Total– 0/20, 2/20 (10%), 2/19 (10%), 17/20 (85%), 13/20 (65%)	$P < 0.05$ (highest two) $P < 0.01$ (trend)	
		Total thyroid gland tumours: 3/20 (15%), 2/20 (10%), 8/19 (40%), 6/20 (30%), 9/20 (45%)	$P < 0.05$ (highest) $P < 0.01$ (trend)	

Table 3.11 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M) 36 wk Wanibuchi *et al.* (1996)	Pretreatment with BBN[d] 0.05% in drinking-water for 4 wk then 0, 2, 10, 25, 50, or 100 ppm DMA^V in drinking-water for 32 wk Groups: BBN alone, BBN + 2 ppm DMA^V, BBN + 10 ppm DMA^V, BBN + 50 ppm DMA^V, BBN + 100 ppm DMA^V 20/group	Urinary bladder: Papillary/nodular hyperplasias– 14/20 (70%), 13/20 (65%), 14/20 (70%), 18/19 (95%), 20/20 (100%), 20/20 (100%)	$P < 0.05$ (highest two doses)	Age at start, ~6 wk DMA^V purity, 99% Separate 0 and 100 ppm control and DMA^V alone groups were included (12 each) but showed no urinary bladder tumours or preneoplastic lesions Bw, water intake and survival unremarkable Urinary bladder only
		Papillomas– 3/20 (15%), 2/20 (10%), 7/20 (35%), 11/19 (58%), 13/20 (65%), 17/20 (85%)	$P < 0.01$ (highest three doses)	
		Carcinomas– 1/20 (5%), 2/20 (10%), 3/20 (15%), 7/19 (37%), 10/20 (50%), 12/20 (60%)	$P < 0.05$ (third highest dose) $P < 0.01$ (highest two doses)	

[a] Diethylnitrosamine

[b] The organic carcinogen treatment consisted of a single dose of diethylnitrosamine (100 mg/kg, i.p.) at the start of the experiment) and*N*-methyl-*N*-nitrosourea (20 mg/kg, s.c.) on experimental Days 5, 8, 11 and 14. Thereafter, rats received 1,2-dimethylhydrazine (40 mg/kg, s.c.) on Days 18, 22, 26, and 30). During the same period (experimental Days 0–30) the rats received *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (0.05% in the drinking-water Weeks 1 and 2) and *N*-bis(2-hydroxypropyl)nitrosamine (0.1% in the drinking-water, Weeks 3 and 4). Altogether this was defined as DMBDD treatment. Rats received no treatment for 2 wk after DMBDD exposure and before DMA exposure.

[c] For brevity, only significant proliferative lesions are noted for each tissue

[d] *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine

[e] 4-Nitroquinoline

[f] 7,12-dimethylbenz[α]anthracene

[g] Estimated from graphical presentation.

d, day or days; DMA, dimethylarsinic acid; F, female; i.p., intraperitoneal; M, male; NR, not reported; s.c., subcutaneously; wk, week or weeks

Table 3.12 Studies where arsenicals given concurrently with other agents enhance carcinogenesis while having no effect alone in experimental animals

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Tg.AC homozygous (F) 14 wk Germolec *et al.* (1997)	0 or 0.02% As in drinking-water, *ad libitum* throughout experiment 0 or 2.5 μg TPA[a]/mouse in acetone topical to shaved dorsal skin twice/wk, Week 5 and 6 Groups: control, As alone, TPA, As + TPA 20/group	Macroscopic skin papillomas/mouse: none in control or arsenic alone, intermediate in TPA alone (~0.5/mouse),[b] "4-fold higher" (~2.1/mouse)[b] in arsenic + TPA	NR	Age at start, NR Purity, NR Survival unremarkable Specific quantitative microscopic analysis of skin tumours not included but confirmed as papillomas at termination Skin lesions only Incomplete reporting makes independent statistical analysis impossible
Mouse, Tg.AC homozygous (F) 24 wk Germolec *et al.* (1998)	0 or 0.02% As in drinking-water, *ad libitum* throughout experiment 0, 1.25, 2.5 μg TPA/mouse in acetone topical to shaved dorsal skin twice/wk, Week 5 and 6 Groups: control, As alone, 1.25 TPA, 2.5 TPA, As + 1.25 TPA, As + 2.5 TPA 20/group	Macroscopic skin papillomas/mouse: 0 in control, As alone, and 1.25 TPA alone; As + 1.25 TPA maximal ~5/mouse,[b] 2.5 TPA ~3/mouse,[b] in arsenic + 2.5 TPA ~7/mouse[b]	NR	Age at start, 8 wk Purity, NR Survival impacted by high-dose TPA co-treatment but specifics not given Quantitative microscopic analysis of skin tumours not included but confirmed as papillomas at termination Skin lesions only Incomplete reporting makes independent statistical analysis impossible

Table 3.12 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Crl: SKl-*hr*BR (hairless) (F) 29 wk Rossman *et al.* (2001)	0, 10 mg/L sodium arsenite in drinking-water throughout experiment plus topical 1.7 kJ/m² solar irradiation (85% UVB, < 1% UVC, 4% UVA, remainder visible; termed UVR[c]) 3x/wk starting 3 wk after As until termination Groups: control, As alone, UVR alone, As + UVR 5–15; 5 controls	Skin (tumours): Macroscopic and microscopic analysis–0/5, 0/5 (control and As alone)		Age at start, 3wk Purity, NR Survival and bw unremarkable Small control groups
		Macroscopic analysis– Time to first occurrence: As + UVR earlier than UVR	$P < 0.01$	
		Microscopic analysis– Total tumours all mice: 53 (UVR), 127 (As + UVR)		
		Highly invasive squamous cell carcinoma: 14/53 (26%; UVR), 64/127 (50%; As + UVR)	$P < 0.01$	
		Tumour volume: UVR smaller than As + UVR	$P < 0.01$	
Mouse, SKl (hairless), (NR) 29 wk Burns *et al.* (2004)	Experiment 1: 0, 1.25, 2.50, 5.00, 10.0 mg/L sodium arsenite in drinking-water from onset plus topical 0 or 1.0 kJ/m² solar irradiation (UVR[c]) 3x/wk, starting 3 wk after As to termination	Experiment 1: Skin tumours/mouse[d]: 2.4 (UVR), 5.4 (1.25 As + UVR), 7.21 (2.5 As + UVR), 11.1 (5.0 As + UVR), 6.8 (10.0 As + UVR)	[$P < 0.01$ all groups vs UVR alone[e]]	Age, 3 wk Survival and bw unremarkable Specific quantitative microscopic analysis of skin tumours not reported but confirmed as primarily squamous cell carcinomas at termination Experiment 1 shows clear arsenic dose–response in enhancement through 5.0 mg/L by various criteria
	Experiment 2: 10.0 mg/L sodium arsenite in drinking-water from onset plus topical 1.7 kJ/m² UVR[c] 3x/wk starting 3 wk after As to termination	Experiment 2: Skin tumours/mouse:[d] 3.5 (UVR), 9.6 (As + UVR) Skin tumour incidence: 0/10, 0/10 (control and As alone both experiments)	[$P < 0.01$[f]]	

Table 3.12 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Crl: SKl-*hr*BR (hairless) (F) Duration, NR Uddin *et al.* (2005)	0, 5 mg/L sodium arsenite in drinking-water from onset; diet unsupplemented or with added vitamin E (62.5 IU/kg diet; basal 49.0 IU/kg) or *p*-XSC[g] (10 mg/kg diet) from onset. Topical 1.0 kJ/m^2 UVR[c] 3x/wk starting 3 wk after As to termination. Groups: UVR alone, UVR + As, UVR + As + Vitamin E, UVR + As + *p*-XSC[h] 10; 30 controls (UVR)	Macroscopic skin tumours/mouse: 3.60 (UVR alone), 7.00 (UVR + As), 3.27 (UVR + As + Vitamin E), 3.40 (UVR + As + *p*-XSC)	$P < 0.01$ (UVR vs UVR + As) $P < 0.01$ (UVR + As vs UVR + As + either dietary supplement)	Age at start, 3 wk Sodium arsenite, purity (NR), *p*-XSC Purity > 99% Survival and bw unremarkable Small control groups Vitamin E and *p*-XSC added as antioxidants Specific quantitative microscopic analysis of skin tumours not reported but random sampling (10 tumours/group) confirmed primarily squamous cell carcinomas at termination No untreated control or arsenic alone groups included
Mouse, Swiss-bald hairless (M) 25 wk Motiwale *et al.* (2005)	Treatment with 2 mg BA[i] /mL 25 µL topical once/wk for 2 wk Sodium arsenate 0 or 25 mg/L drinking-water for 25 wk Groups: Control, BA, As, BA + As 10/group	Macroscopic skin tumours/mouse: 0, 2.0, 0, 3.2[b] % large papillomas (≥ 3 mm) of total papillomas: 0, 16, 0, 65[d]	$P < 0.05$ (As + BA vs BA) $P < 0.05$ (As + BA vs BA)	Age at start, 8 wk Purity, NR Survival unremarkable Small group sizes Quantitative microscopic skin tumour incidence or multiplicity not reported though histologically confirmed

[a] 12-*O*-tetradecanoyl-13-acetate.
[b] Estimated from graphical presentation. No descriptive statistics included.
[c] UVR as defined inRossman *et al.* (2001) above.
[d] Data included descriptive statistics.
[e] Using Dunnett's multiple comparison test and not including arsenic alone and untreated control groups
[f] Using Student's*t*-test.
[g] 1,4-Phenyl*bis*(methylene)selenocyanate a synthetic organoselenium compound.
[h] Some control groups are not discussed for the sake of brevity (UVR + Vitamin E and UVR +*p*-XSC).
[i] 9,10-dimethyl-1,2-benzanthracene.
F, female; M, male; NR, not reported; wk, week or weeks

of age, although arsenic treatment alone had no effect, it markedly increased the multiplicity of squamous cell carcinoma when combined with TPA compared to TPA alone (Waalkes *et al.*, 2008; see Table 3.13).

Prenatal sodium arsenite exposure via maternal drinking-water when combined with postnatal topical TPA exposure increased the liver tumour incidence and multiplicity in an arsenic-dose-related fashion (female offspring), and lung tumours (male offspring) compared to controls; effects not seen with TPA or arsenic alone (Waalkes *et al.*, 2004). Prenatal arsenic exposure followed by postnatal diethylstilbestrol increased uterine carcinoma, vaginal carcinoma, urinary bladder total proliferative lesions, and liver tumours in female offspring compared to controls; effects not seen with diethylstilbestrol or arsenic alone. In female offspring, prenatal arsenic exposure followed by postnatal tamoxifen administration similarly increased urinary bladder total proliferative lesions (Waalkes *et al.*, 2006a).

In male offspring, prenatal arsenic exposure followed by postnatal diethylstilbestrol increased the liver tumour response and urinary bladder total proliferative lesions effects when compared to controls; effects not seen with diethylstilbestrol or arsenic alone. In male offspring, prenatal arsenic exposure followed by postnatal tamoxifen increased liver tumour response, urinary bladder total tumours, and urinary bladder total proliferative lesions (Waalkes *et al.*, 2006b).

3.5.2 Rat

Rats that underwent partial hepatectomy followed by diethylnitrosamine injection and one week later by oral administration of sodium arsenite in the drinking-water for approximately 24 weeks showed an increased incidence of renal tumours, but arsenic treament alone had no effect (Shirachi *et al.*, 1983).

In a comprehensive study, rats were given an initial pretreatment with a mixture of organic carcinogens (including diethylnitrosamine, *N*-methyl-*N*-nitrosourea, 1,2-dimethylhydrazine, *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine, and *N*-bis(2-hydroxypropyl)nitrosamine) by various routes, no treatment for 2 weeks and then DMA^V (at four levels) in the drinking-water for 24 weeks, rats developed an increased incidence of tumours of urinary bladder with the combined carcinogen treatment and arsenical (Yamamoto *et al.*, 1995).

In another study in rats, *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine in the drinking-water was used as an initiator for 4 weeks followed by four levels of DMA^V for 32 weeks, and the combined treatment increased urinary bladder hyperplasia, papilloma, and carcinoma, but the arsenical treatment alone had no effect (Wanibuchi *et al.*, 1996).

3.6 Gallium arsenide

A single study (NTP, 2000) was judged to provide evidence for the carcinogenicity of gallium arsenide in rodents. In this report, $B6C3F_1$ mice and F344 rats were exposed via inhalation to various levels of gallium arsenide particulate for up to ~2 years, and the tumour response was assessed in various tissues (see Table 3.14).

3.6.1 Mouse

No treatment-related tumours were observed, but in both males and females, dose-related increases in the incidence in lung epithelial alveolar hyperplasia were reported.

3.6.2 Rat

In female rats, dose-related responses were reported for the incidence of lung alveolar/bronchiolar tumours and atypical hyperplasia

Table 3.13 Studies where arsenic given before another agent enhances carcinogenesis while having no effect alone in experimental animals

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Tg.AC (M, F) Homozygous 40 wk (*postpartum*) Waalkes *et al.* (2008)	Maternal exposure: 0, 42.5, 85 ppm arsenic in drinking-water, *ad libitum*, gestation Day 8–18	Skin (tumours): Papillomas/mouse[a]– 0.5 (control), 0.9 (42.5 As), 0.12 (85 As), 17 (TPA[b]), 17 (42.5 As + TPA), 11 (85 As + TPA)	$P < 0.05$ (all TPA groups vs control; TPA alone vs 85As + TPA)	Age, 4 wk (offspring) Purity, NR Litters culled at 4 d *postpartum* to no more than 8 pups 10 pregnant mice used to randomly derive each group Maternal water consumption and body unaltered Offspring weaned at 4 wk Offspring bw unaltered by arsenic All skin tumours were histopathologically diagnosed for stage and number per animal Some mice were killed because of tumour burden during experiment but were not lost to observation Only skin tumours reported
	Offspring exposure:[a] TPA, 2 µg/0.1 mL acetone, topical twice/wk, applied to shaved dorsal skin, 4–40 wk of age (36 wk of TPA exposure)	Squamous cell carcinomas/ mouse:[a] 0.04 (control), 0.06 (42.5 As), 0.04 (85 As), 0.57 (TPA), 1.31 (42.5 As + TPA), 1.49 (85 As + TPA)	$P < 0.05$ (all TPA groups vs control; all As + TPA groups vs TPA alone $P < 0.01$ (trend with As in TPA-treated mice)	
	Offspring groups (M, F):[c] Without TPA: (0, 42.5, 85 ppm arsenic) With TPA: (0, 42.5, 85 ppm arsenic) 50/group	Incidence of mice with 3 or more squamous cell carcinomas: 0/49 (control), 0/47 (42.5 As), 0/48 (85 As), 1/47 (2%; TPA), 9/48 (19%; 42.5 As + TPA), 14/49 (29%; 85 As + TPA)	$P < 0.05$ (all TPA + As groups vs control or TPA alone) $P < 0.01$ (trend with As in TPA-treated mice)	

[a] Manuscript included descriptive statistics.
[b] 12-*O*-tetradecanoyl-13-acetate.
[c] Because initial analysis of tumours showed no gender-based differences between similarly treated groups of males and females, they were pooled for final assessment and are reported as such. Initial groups were made up of 25 M and 25 F mice.
bw, body weight; F, female; M, male; NR, not reported; vs; versus; wk, week or weeks

Table 3.14 Studies of cancer in experimental animals exposed to gallium arsenide (inhalation exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M, F) 105 wk for M 106 wk for F NTP (2000)	0, 0.1, 0.5, 1.0 mg/m^3 6 h/d, 5 d/wk 50/group/sex	**Females** Lung (epithelial alveolar hyperplasias):2/50 (4%), 5/50 (10%), 27/50 (54%), 43/50 (86%) Lung[a] (adenomas or carcinomas): 7/50 (14%), 4/50 (8%), 4/50 (8%), 6/50 (12%) **Males** Lung (epithelial alveolar hyperplasias):4/50 (8%), 9/50 (18%), 39/50 (78%), 45/50 (90%) Lung[a] (adenomas or carcinomas): 15/50 (30%), 14/50 (28%), 16/50 (32%), 13/50 (26%)	 $P \leq 0.01$ (high dose) $P \leq 0.01$ (mid-dose) NS $P \leq 0.01$ (high dose) $P \leq 0.01$ (mid-dose) NS	Age at start, 6 wk Purity > 98% MMAD, 0.9–1.0 μm GSD, 1.8–1.9 μm Chamber controls used No reduced bw with treatment Survival unaltered No increases in tumour incidence
Rat, F344 (F) 105 wk NTP (2000)	0, 0.01, 0.1, 1.0 mg/m^3 6 h/d, 5 d/wk 50/group/sex	**Females** Lung[a] (adenomas): 0/50, 0/50, 2/50 (4%), 7/50 (14%) Lung (carcinomas): 0/50, 0/50, 2/50 (4%), 3/50 (6%) Lung (adenomas or carcinomas): 0/50, 0/50, 4/50 (8%), 9/50 (18%) Adrenal medulla:[b] 4/50 (8%), 6/49 (12%), 6/50 (12%), 13/49 (27%) Mononuclear cell leukaemia: 22/50 (44%), 21/50 (42%), 18/50 (36%), 33/50 (66%) **Males** Lung (atypical hyperplasias): 0/50, 2/49 (4%), 5/50 (10%), 18/50 (36%) Lung[a] (adenomas): 1/50 (2%), 0/49, 3/50 (6%), 2/50 (4%) Lung (carcinomas): 2/50 (4%), 0/49, 2/50 (4%), 1/50 (2%) Lung (adenomas or carcinomas): 3/50 (6%), 0/49, 5/50 (10%), 3/50 (6%)	 $P \leq 0.01$ (high dose) $P \leq 0.01$ (trend) NS $P \leq 0.01$ (high dose) $P \leq 0.01$ (trend) $P \leq 0.01$ (high dose) $P \leq 0.01$ (trend) $P \leq 0.05$ (high dose) $P \leq 0.01$ (trend) $P \leq 0.01$ (high dose) $P \leq 0.05$ (mid-dose) NS NS NS	Age at start, 6 wk Purity > 98% MMAD, 0.9–1.0 μm GSD, 1.8–1.9 μm Chamber controls used Minimal decrease in body weight at high dose in second yr Survival unaltered No increases in tumour incidence in males

[a] All lung tumours were of avelolar/bronchiolar origin.
[b] All tumours were benign pheochromocytoma except one which was malignant in the low-dose group.
d, day or days; F, female; h, hour or hours; M, male; NS, not significant; wk, week or weeks; yr, year or years

of the alveolar epithelium. In male rats, though treatment-related tumours were not observed, a dose-related increase in the incidence of atypical hyperplasia of the lung alveolar epithelium occurred. Atypical hyperplasia of the lung alveolar epithelium is considered potentially preneoplastic. In the female rats, dose-related increases in the incidence of adrenal medulla pheochromocytomas and an increase in mononuclear cell leukaemia at the highest dose were also reported (NTP, 2000).

3.6.3 Hamster

Another study using intratracheal instillation of gallium arsenide in hamsters (Ohyama *et al.*, 1988) was judged inadequate due to critical design flaws (short duration, small groups, etc.) with no indication of tumours.

3.7 Synthesis

Oral administration of sodium arsenate and DMA^{V} induced lung tumours in mice. Calcium arsenate induced lung tumours in hamsters by oral and intratracheal administration. Pre- and postnatal exposure in mice to arsenic trioxide, through subcutaneous injections (maternal and postnatal), induced lung tumours in the offspring. Transplacental exposure via maternal oral exposure in mice to sodium arsenite during gestation induced lung, liver, ovary and adrenal tumours in the offspring in several studies, and the uterus in one study. Early life transplacental and perinatal exposure to sodium arsenite appears to be a time of particular sensitivity in terms of carcinogenesis.

Oral exposure to DMA^{V} induced urinary bladder tumours in several studies in rats and among studies in mice, only one showed negative results. Oral trimethylarsine induced liver tumours in rats. Chronic oral exposure to MMA^{V} did not produce tumours in rats and mice. [The Working Group considered that previous traditional bioassays for arsenicals for adult rodents were frequently negative in their final evaluations.]

Inhalation of gallium arsenide causes lung and adenal tumours in rats but not in mice.

In multiple studies, initiating, promoting or co-carcinogenic activity was demonstrated in the urinary bladder, skin, female reproductive tract, kidney, lung, liver and thyroid after exposure to inorganic arsenicals or DMA^{V} in drinking-water or by transplacental exposure.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

Most inorganic arsenic compounds are readily absorbed after oral exposure (about 80–90% for soluble compounds, and a smaller percentage for less soluble compounds), less well absorbed after inhalation (better for small particulates and soluble arsenicals), and least well absorbed after dermal exposure (NRC, 1999; IARC, 2004). Large airborne arsenic-containing particulates that are deposited in the upper airways may also be absorbed in the intestine if they are later swallowed. Hamsters exposed to gallium arsenide by the oral route or by intratracheal instillation showed the presence of As^{III} in blood and urine, but the majority of the gallium arsenide was excreted in faeces, indicating that absorption was limited by its insolubility. Absorption was about 30 times higher after intratracheal installation than by the oral route (Carter *et al.*, 2003).

The transport of As^{V} is thought to take place via phosphate transporters (Csanaky & Gregus, 2001). The sodium-coupled phosphate transporter NaPi-IIb may be responsible in part for the intestinal and hepatic uptake of As^{V} (Villa-Bellosta & Sorribas, 2008). As^{III} enters the cell by aquaglyceroporins 9 and 7 (Liu *et al.*, 2004),

although another major pathway for the uptake of As^{III} and MMA^{III} (see below) is probably via hexose permeases (Rosen & Liu, 2009). Because As^{V} is rapidly reduced to As^{III} once it enters the cell (Carter *et al.*, 2003), the faster rate of cellular uptake of As^{III}, compared with As^{V}, may be part of the explanation for the greater toxicity of As^{III} (Bertolero *et al.*, 1987; Dopp *et al.*, 2004). However, the much higher chemical reactivity of As^{III}, compared to that of As^{V} is the major explanation. Some data suggests that glyceraldehyde 3-phosphate dehydrogenase (GAPDH) functions as a cytosolic As^{V} reductase *in vivo* (Németi *et al.*, 2006), although there are other candidate enzymes for this reaction (Aposhian *et al.*, 2004). As^{III} can react with cellular glutathione (GSH), either spontaneously or enzymatically, to form the tri-glutathione complex $As(SG)_3$ (Leslie *et al.*, 2004; Rey *et al.*, 2004).

As^{III} is metabolized by stepwise methylation, mainly in the liver. Although some details of inorganic arsenic metabolism remain uncertain (Aposhian & Aposhian, 2006), it is clear that the enzyme arsenic (+3 oxidation state) methyltransferase (AS3MT) is involved (Thomas *et al.*, 2007). Two schemes have been proposed for the methylation.

Reduction: As^{V} + thiol → As^{III}
Oxidative methylation: As^{III} + SAM → monomethylarsonate (MMA^{V})
Reduction: MMA^{V} + thiol → MMA^{III}
Oxidative methylation: MMA^{III} + SAM → dimethylAs^{V} (DMA^{V})
Reduction: DMA^{V} + thiol → DMA^{III}

Scheme 1: Inorganic arsenic metabolic pathway in mammals. As^{III} methylation is catalysed by AS3MT using *S*-adenosylmethionine (SAM) as a methyl donor and thioredoxin (or, less efficiently, other thiols such as glutaredoxin or lipoic acid) as a reductant. MMA^{III}: monomethylarsonous acid; MMA^{v}: monomethylarsonic acid; DMA^{III}: dimethylarsinous acid; DMA^{v}: dimethylarsinic acid

$As(SG)_3$ + SAM → MMA^{III} $(SG)_2$
MMA^{III} $(SG)_2$ + SAM → DMA^{III} (SG)

Scheme 2: The use of $As(SG)_3$ (tri-glutathione complex) as a substrate for methylation (Hayakawa *et al.*, 2005). Each of the glutathione (GSH) complexes can also decompose to yield GSH and MMA^{III} or DMA^{III}, which can then form MMA^{V} and DMA^{V}, respectively.

Neither reaction scheme necessarily goes to completion *in vivo*.

Evidence shows that exposure to arsine gas (AsH_3) results in the same metabolites as described above, but arsenobetaine found in seafood does not get metabolized in humans (Crecelius, 1977; Luten *et al.*, 1982; Le *et al.*, 1993, 1994; Buchet *et al.*, 1996; Schmeisser *et al.*, 2006). Information is not currently available on the other organo-arsenic compounds in seafood (Lai *et al.*, 2004).

Dimethylthioarsinic acid ($DMMTA^{V}$) and dimethyldithioarsinic acid ($DMDTA^{V}$) can be formed from DMA^{III} in red blood cells, and possibly in other cells (Naranmandura *et al.*, 2007; Suzuki *et al.*, 2007). These compounds have been observed in the urine of arsenic-exposed individuals (Raml *et al.*, 2007). They may have been misidentified as MMA^{III} and DMA^{III} in most studies (Hansen *et al.*, 2004).

Most organisms detoxify inorganic arsenic by cellular efflux (Rosen & Liu, 2009). In fibroblasts and other non-methylating cells, protection against arsenic takes place by specific mechanisms for $As(SG)_3$ efflux catalysed by multidrug-resistance-associated protein-transport ATPases MRP1 and MRP2, and maybe others (Kala *et al.*, 2000; Leslie *et al.*, 2004). These efflux pumps may also remove methylated arsenic–glutathione (As–GSH) complexes.

The rat is not a good model for the human in studying the toxicokinetics of arsenic because rat haemoglobin has a much higher affinity for trivalent arsenic species compared with human haemoglobin (Lu *et al.*, 2004). In mice, chronic

exposure (12 weeks) to As^{V} via drinking-water led to total tissue arsenic accumulation in the following ranking: kidney > lung > bladder > > > skin > blood > liver (Kenyon *et al.*, 2008). Monomethylated arsenic species (MMAs) predominated in the kidney, and dimethylated arsenic species (DMAs) predominated in the lung. Urinary bladder and skin had about equal ratios of inorganic arsenic and DMAs. The proportions of different arsenic species in urinary bladder tissue did not match those in urine.

In a study of intratracheal instillation of gallium arsenide, although substantial levels of arsenic were detected in blood and urine, no gallium was detected except for the amount that was left in the lung (Carter *et al.*, 2003).

Human exposure to arsenic is mainly via drinking-water. Trivalent arsenicals are eliminated via the bile, and pentavalent arsenicals are mainly eliminated by urinary excretion (Gregus *et al.*, 2000; Kala *et al.*, 2000; Csanaky & Gregus, 2002). Most population groups exposed mainly via drinking-water excrete 60–70% DMAs and 10–20% MMAs, the remainder 10–30% being inorganic compounds (Vahter, 2000). [The Working Group noted that this study did not include thiolated compounds, which had not yet been discovered.] Interindividual differences in methylation patterns may reflect genetic polymorphisms in AS3MT, and/or variability in the activities of different reductants (Thomas *et al.*, 2007).

4.2 Genetic and related effects

Arsenicals do not react directly with DNA, but cells treated with low concentrations of trivalent arsenicals show increased oxidative DNA damage (Wang *et al.*, 2002; Schwerdtle *et al.*, 2003; Shi *et al.*, 2004; Ding *et al.*, 2005; Wang *et al.*, 2007a). As^{III} and MMA^{III} are equally potent inducers of oxidative DNA damage in human urothelial cells, where they are equally toxic (Wang *et al.*, 2007a). Cytotoxic concentrations of trivalent arsenicals also cause DNA strand breaks and/or alkali-labile sites (Kligerman *et al.*, 2003; Klein *et al.*, 2007). In mice, DMA^{V} causes lung-specific DNA damage attributed to the DMA peroxy radical $(CH_3)_2AsOO$ (Yamanaka & Okada, 1994), which can also induce DNA strand breaks and DNA–protein crosslinks in cultured cells (Tezuka *et al.*, 1993).

Gallium arsenide and other arsenicals are not mutagenic in the Ames test (NTP, 2000; IARC, 2004). There was no increase in frequency of micronucleated erythrocytes in mice exposed to gallium arsenide by inhalation for 14 weeks (NTP, 2000).

Despite the fact that low (non-toxic) concentrations of trivalent arsenicals cause oxidative DNA damage such as 8-hydroxy-2′-deoxyguanosine, which is expected to cause G→T transversions, neither As^{III}, MMA^{III} nor DMA^{III} are significant point mutagens (Rossman, 2003; Klein *et al.*, 2007). This may be due to the efficient removal of oxidative DNA lesions (Fung *et al.*, 2007; Pu *et al.*, 2007b). At toxic concentrations, As^{III} increased large-deletion mutations in human/hamster hybrid cells through a mechanism mediated by reactive oxygen species (Hei *et al.*, 1998). MMA^{III} and DMA^{III} are weakly mutagenic in mouse lymphoma L5178Y cells, but only at toxic concentrations, and yield mostly deletions (Moore *et al.*, 1997; Kligerman *et al.*, 2003).

Using a transgenic cell line that readily detects deletions as well as point mutations, statistically significant mutagenesis was never observed for DMA^{III}, and was only seen for As^{III} or MMA^{III} at toxic concentrations. MMA^{III} yielded a mutant fraction about 4-fold over background at 11% survival, and 79% of these mutants were deletions (Klein *et al.*, 2007).

As^{III}, MMA^{III}, and DMA^{III} can induce chromosomal aberrations *in vitro* (Oya-Ohta *et al.*, 1996; Kligerman *et al.*, 2003). Statistically significant increases in chromosomal aberrations occur only at toxic doses (Klein *et al.*, 2007), except as a secondary effect of genomic

instability in long-term, low-dose treatment protocols (Sciandrello *et al.*, 2004). An analysis of micronuclei induced by As^{III} in human fibroblasts shows that at lower (relatively non-toxic) doses, As^{III} acts as an aneugen by interfering with spindle function and causing micronuclei with centromeres, but at high (toxic) doses, it acts as a clastogen, inducing micronuclei without centromeres (Yih & Lee, 1999). Aneuploidy is seen after treatment with As^{III} concentrations lower than those that cause chromosomal aberrations (Yih & Lee, 1999; Ochi *et al.*, 2004; Sciandrello *et al.*, 2002, 2004). Aneuploidy associated with disruption of spindle tubulin has been reported in other cells treated with arsenicals (Huang & Lee, 1998; Kligerman & Tennant, 2007; Ramírez *et al.*, 2007). Disrupted mitotic spindles and induced persistent aneuploidy were maintained even 5 days after As^{III} removal (Sciandrello *et al.*, 2002). Humans exposed to high concentrations of inorganic arsenic in drinking-water also show increased micronuclei in lymphocytes, exfoliated bladder epithelial cells and buccal mucosa cells, and sometimes chromosomal aberrations and sister chromatid exchange in whole-blood lymphocyte cultures (Basu *et al.*, 2001). Micronuclei and chromosomal aberrations are also induced in mice after intraperitoneal treatment with As^{III} (IARC, 2004).

Long-term low-dose treatment of human osteosarcoma cells with As^{III} (but not MMA^{III}) resulted in increased mutagenesis and transformation as a secondary effect of genomic instability (Mure *et al.*, 2003). In Chinese hamster V79–13 cells grown in the presence of low concentrations of As^{III}, genomic instability (measured by chromosomal aberrations in later generations) followed earlier changes in DNA methylation and aneuploidy (Sciandrello *et al.*, 2002, 2004). Other studies report gene amplification (Lee *et al.*, 1988; Rossman & Wolosin, 1992), and changes in gene expression, e.g. by DNA methylation changes (Liu *et al.*, 2006b; Klein *et al.*, 2007; Reichard *et al.*, 2007; Liu & Waalkes, 2008). Alterations of DNA methylation, along with histone modification, were seen in cells treated with As^{III} and MMA^{III} (Jensen *et al.*, 2008; Zhou *et al.*, 2008). Global DNA hypomethylation, along with hypermethylation of specific genes, was demonstrated in several As^{III}-transformed cells (Benbrahim-Tallaa *et al.*, 2005a; Liu & Waalkes, 2008). Oxidative damage to DNA has been shown to cause changes in DNA methylation (Cerda & Weitzman, 1997), suggesting a mechanism by which As^{III} may induce this effect. Changes in DNA methylation patterns could also result from altered SAM pools or downregulation of DNA methyltransferases (Hamadeh *et al.*, 2002; Benbrahim-Tallaa *et al.*, 2005a; Reichard *et al.*, 2007; Liu & Waalkes, 2008). Altered DNA methylation has also been observed in arsenic-exposed humans (Chanda *et al.*, 2006; Marsit *et al.*, 2006).

Although not a mutagen, As^{III} can enhance the mutagenicity of other agents (Rossman, 2003; Danaee *et al.*, 2004; Fischer *et al.*, 2005). Co-mutagenesis may occur by interference with both nucleotide-excision repair and base-excision repair (Hartwig *et al.*, 2002; Rossman, 2003; Danaee *et al.*, 2004; Wu *et al.*, 2005; Shen *et al.*, 2008). Nucleotide-excision repair was blocked in human fibroblasts with the following potency: $MMA^{III} > DMA^{III} > As^{III}$ (Shen *et al.*, 2008). As^{III} is not a very effective inhibitor of DNA-repair enzymes (Snow *et al.*, 2005). Rather, it appears to affect DNA-damage signalling events that control DNA repair. One of these is poly(ADP-ribose) polymerase (PARP) (Hartwig *et al.*, 2003; Qin *et al.*, 2008). PARP-1, the major PARP, is involved in base-excision repair by interacting with DNA-repair protein XRCC1, DNA polymerase β, and DNA ligase ^{III}. This might explain the inhibition of the ligation step of base-excision repair by As^{III} (Li & Rossman, 1989). MMA^{III} and DMA^{III} are more effective PARP inhibitors than is As^{III} (Walter *et al.*, 2007). The inhibition of PARP (and other proteins such as XPA) may be

mediated by the displacement of zinc (Zn) at Zn fingers (Schwerdtle *et al.*, 2003; Qin *et al.*, 2008).

Another important signal pathway affected by As^{III} is that mediated by tumour-suppressor gene *Tp53*. As^{III} was shown to prevent the activation of the P53 protein and the downstream expression of p21 after genotoxic insult (Vogt & Rossman, 2001; Tang *et al.*, 2006; Shen *et al.*, 2008). This has the effect of overriding the growth arrest at G1 (normally an opportunity for DNA repair to take place before DNA replication) in cells with DNA damage, and might explain part of the co-mutagenic effect (Vogt & Rossman, 2001; Hartwig *et al.*, 2002; Mudipalli *et al.*, 2005). p53 is also required for proficient global nucleotide-excision repair (Ferguson & Oh, 2005). The inhibition of thioredoxin reductase by As^{III}, MMA^{III} and DMA^{III} (Lin *et al.*, 1999) would cause the accumulation of oxidized thioredoxin, which may be partially responsible for p53 malfunction, as is shown in yeast (Merwin *et al.*, 2002). The upregulation of positive growth genes such as cyclin D by low concentrations of As^{III} would also tend to drive cells to cycle inappropriately (Trouba *et al.*, 2000; Vogt & Rossman, 2001; Luster & Simeonova, 2004).

In addition to inhibiting particular proteins, As^{III} (at slightly toxic concentrations) can downregulate expression of some DNA repair genes (Hamadeh *et al.*, 2002; Andrew *et al.*, 2006; Sykora & Snow, 2008). However, very low, non-toxic concentrations, may have the opposite effect of upregulating DNA repair, concomitant with antioxidant defenses (Snow *et al.*, 2005; Sykora & Snow, 2008).

4.3 Co-carcinogenic and *in utero* carcinogenic effects

There are several non-genotoxic actions of As^{III} (sometimes demonstrated also for its trivalent metabolites) that may contribute to arsenic-induced carcinogenesis. The effects of As^{III} on preventing blockage of the cell cycle after genotoxic insult by a second agent were discussed above. In addition, low concentrations of As^{III} in the absence of a second agent can also stimulate cell proliferation *in vitro* (Germolec *et al.*, 1997; Trouba *et al.*, 2000; Vogt & Rossman, 2001; Benbrahim-Tallaa *et al.*, 2005b; Komissarova *et al.*, 2005), and *in vivo* (Germolec *et al.*, 1998; Burns *et al.*, 2004; Luster & Simeonova, 2004). The concentration-dependent increase in proliferation of human keratinocytes after 24 hours of treatment with arsenicals followed the potency trend: $DMA^{III} > MMA^{III} > As^{III}$ (Mudipalli *et al.*, 2005). As^{III} upregulates pro-growth proteins such as cyclin D1, c-myc, and E2F-1 (Trouba *et al.*, 2000; Vogt & Rossman, 2001; Ouyang *et al.*, 2007). The increased proliferation in mouse skin by As^{III} alone (in drinking-water) is not sufficient to induce skin cancer (Burns *et al.*, 2004), but may contribute to its co-carcinogenesis with solar ultraviolet. As^{III} was found to block the differentiation of skin cells, resulting in increased numbers of keratinocyte stem cells, the cells that proliferate (Patterson & Rice, 2007; Waalkes *et al.*, 2008). Because tumours may arise from stem cells, this would increase the pool of target cells for cancer of the skin.

Another mechanism for arsenic-related carcinogenesis might be acquired resistance to apoptosis. Long-term growth of human skin cells (HaCaT) in the presence of low concentrations of As^{III} resulted in cells with a generalized resistance to apoptosis (Pi *et al.*, 2005). This may allow the survival of cells with DNA damage, thus facilitating tumorigenesis. Even short-term exposure to As^{III} affected the apoptotic response to solar UV in a mouse keratinocyte cell line (Wu *et al.*, 2005) or to UVB in normal human keratinocytes (Chen *et al.*, 2005b). It is possible that the loss of the P53 function partially mediates the reduction in apoptotic response (Chen *et al.*, 2005b).

Numerous studies report increased inflammation after As^{III} exposure (NRC, 1999; Straub

et al., 2007). The transcription factor NF-κB is involved in the inflammatory response, and As^{III} causes oxidant-dependent activation of NF-κB (Barchowsky *et al.*, 1999). Activation of the NF-κB inflammatory signalling pathway was seen in infants born to As^{III}-exposed mothers in Bangladesh (Fry *et al.*, 2007).

As^{III} can disrupt the signalling of the estrogen receptor, glucocorticoid receptor, and of other steroids *in vivo* and *in vitro* (Benbrahim-Tallaa *et al.*, 2005b, 2007; Liu *et al.*, 2007; Davey *et al.*, 2008). Submicromolar concentrations of As^{III} stimulate the transcription of several steroid receptors, but slightly higher concentrations (1–3 μM) are inhibitory (Bodwell *et al.*, 2006). Exposure of mice *in utero* to As^{III} in a protocol leading to hepatocarcinogenesis resulted in altered expression of numerous genes involved in estrogen signalling or steroid metabolism, as well as hypomethylation of estrogen receptor α (Liu & Waalkes, 2008).

Angiogenesis, which provides a blood supply to developing tumours, is stimulated by very low concentrations of As^{III} (Mousa *et al.*, 2007; Straub *et al.*, 2007). This activity can be blocked by selenium compounds (Mousa *et al.*, 2007), which also blocks As^{III}-induced co-carcinogenesis with UV and delays mutagenesis (Uddin *et al.*, 2005).

Many of these effects depend on altered gene expression that can result from genetic and epigenetic effects discussed above. Changes in gene expression by As^{III} can also be mediated by the alteration of iRNA patterns (Marsit *et al.*, 2006). Some short-term changes in gene expression (e.g. changes in the expression of DNA-repair proteins or DNA methyltransferases) can result in long-term changes. Genome-wide changes in gene expression and signal transduction induced by arsenicals have been reported in several publications (Su *et al.*, 2006; Kumagai & Sumi, 2007; Ghosh *et al.*, 2008).

4.4 Synthesis

In the human body, inorganic arsenic compounds are converted to As^{III} and As^{V}. As^{V} is rapidly converted to As^{III}. As^{III} species are more toxic and bioactive than are As^{V} species, both because of the greater chemical reactivity of As^{III}, and because As^{III} enters cells more easily.

For inorganic arsenic and its metabolites, the evidence points to weak or non-existent direct mutagenesis, which is seen only at highly cytotoxic concentrations. On the other hand, long-term, low-dose exposure to inorganic arsenic – more relevant to human exposure – is likely to cause increased mutagenesis as a secondary effect of genomic instability, perhaps mediated by increased levels of reactive oxygen species, as well as co-mutagenesis with other agents. The major underlying mechanisms observed at low concentrations include the rapid induction of oxidative DNA damage and DNA-repair inhibition, and slower changes in DNA-methylation patterns, aneuploidy, and gene amplification. Gene amplification, altered DNA methylation, and aneuploidy lead to altered gene expression, and genomic instability. Inhibition of DNA repair leads to co-mutagenicity as well. These effects are consistent with the animal carcinogenicity data, in which As^{III} is a transgenerational carcinogen – with exposure being present during many cell generations – and in results observed in co-carcinogenicity studies.

For bladder tumours induced by high doses of DMA^{V} in the rat, the mechanism is likely to involve sustained cytotoxicity followed by stress-related cell proliferation, leading to genomic instability.

Inflammation and cytotoxicity may play a role in lung tumours induced by gallium arsenide in female rats.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of mixed exposure to inorganic arsenic compounds, including arsenic trioxide, arsenite, and arsenate. Inorganic arsenic compounds, including arsenic trioxide, arsenite, and arsenate, cause cancer of the lung, urinary bladder, and skin. Also, a positive association has been observed between exposure to arsenic and inorganic arsenic compounds and cancer of the kidney, liver, and prostate.

There is *sufficient evidence* in experimental animals for the carcinogenicity of dimethylarsinic acid, calcium arsenate, and sodium arsenite.

There is *limited evidence* in experimental animals for the carcinogenicity of sodium arsenate, gallium arsenide, arsenic trioxide, and trimethylarsine oxide.

There is *inadequate evidence* in experimental animals for the carcinogenicity of monomethylarsonic acid and arsenic trisulfide.

In view of the overall findings in animals, there is *sufficient evidence* in experimental animals for the carcinogenicity of inorganic arsenic compounds.

Arsenic and inorganic arsenic compounds are *carcinogenic to humans (Group 1)*.

Dimethylarsinic acid and monomethylarsonic acid are *possibly carcinogenic to humans (Group 2B)*.

Arsenobetaine and other organic arsenic compounds not metabolized in humans, are *not classifiable as to their carcinogenicity to humans (Group 3)*.

The Working Group made the overall evaluation on 'arsenic and inorganic arsenic compounds' rather than on some individual arsenic compounds, based on the combined results of epidemiological studies, carcinogenicity studies in experimental animals, and data on the chemical characteristics, metabolism, and modes of action of carcinogenicity.

Elemental arsenic and inorganic arsenic species share the same metabolic pathway: arsenate→arsenite→methylarsonate→dimethylarsenite. Thus, independent of the mechanisms of the carcinogenic action, and independent of which of the metabolites is the actual ultimate carcinogen, different inorganic arsenic species should be considered as carcinogenic.

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BERYLLIUM AND BERYLLIUM COMPOUNDS

Beryllium and beryllium compounds were considered by previous IARC Working Groups in 1971, 1979, 1987, and 1993 (IARC, 1972, 1980, 1987, 1993). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Synonyms and molecular formulae for beryllium, beryllium–aluminium and beryllium–copper alloys, and certain beryllium compounds are presented in Table 1.1. The list is not exhaustive, nor does it comprise necessarily the most commercially important beryllium-containing substances; rather, it indicates the range of beryllium compounds available.

1.2 Chemical and physical properties of the agents

Beryllium (atomic number, 4; relative atomic mass, 9.01) is a metal, which belongs to Group IIA of the Periodic Table. The oxidation state of beryllium compounds is +2. Selected chemical and physical properties of beryllium, beryllium–aluminium and beryllium–copper alloys, and various beryllium compounds can be found in the previous *IARC Monograph* (IARC, 1993).

Beryllium is the lightest of all solid chemically stable substances, and has an unusually high melting-point. It has a very low density and a very high strength-to-weight ratio. Beryllium is lighter than aluminium but is greater than 40% more rigid than steel. It has excellent electrical and thermal conductivities. Its only markedly adverse feature is relatively pronounced brittleness, which restricts the use of metallic beryllium to specialized applications (WHO, 1990).

Because of its low atomic number, beryllium is very permeable to X-rays. Neutron emission after bombardment with α or γ rays is the most important of its nuclear physical properties, and beryllium can be used as a neutron source. Moreover, its low neutron absorptiveness and high-scattering cross-section make it a suitable moderator and reflector in structural materials in nuclear facilities; where most other metals absorb neutrons emitted during the fission of nuclear fuel, beryllium atoms only reduce the energy of such neutrons, and reflect them back into the fission zone (Ballance *et al.*, 1978; Newland, 1984; WHO, 1990).

The chemical properties of beryllium differ considerably from those of the other alkaline earths, but it has several chemical properties in common with aluminium. Like aluminium, beryllium is amphoteric and shows very high affinity for oxygen; on exposure to air or water vapour, a thin film of beryllium oxide forms on

Table 1.1 Chemical names (CAS names are in italics), CAS numbers, synonyms, and molecular formulae of beryllium and beryllium compounds

Chemical name	CAS Reg. No[a]	Synonyms	Formula
Beryllium metal	7440-41-7	*Beryllium*; beryllium element; beryllium metallic	Be
Beryllium–aluminum alloy[b]	12770-50-2	*Aluminium alloy, nonbase, Al,Be*; aluminium–beryllium alloy	Al.Be
Beryllium–copper alloy[c]	11133-98-5	*Copper alloy, base, Cu,Be*; copper–beryllium alloy	Be.Cu
Beryl	1302-52-9	Beryllium aluminosilicate; beryllium aluminium silicate	$Al_2Be_3(SiO_3)_6$
Beryllium chloride	7787-47-5	Beryllium dichloride	$BeCl_2$
Beryllium fluoride	7787-49-7 (12323-05-6)	Beryllium difluoride	BeF_2
Beryllium hydroxide	13327-32-7 (1304-49-0)	Beryllium dihydroxide	$Be(OH)_2$
Beryllium sulfate	13510-49-1	*Sulfuric acid, beryllium salt (1:1)*	$BeSO_4$
Beryllium sulfate tetrahydrate	7787-56-6	*Sulfuric acid, beryllium salt (1:1), tetrahydrate*	$BeSO_4.4H_2O$
Beryllium oxide	1304-56-9	Beryllia; beryllium monoxide	BeO
Beryllium carbonate basic[d]	1319-43-3	*Carbonic acid, beryllium salt, mixture with beryllium hydroxide (Be(OH)$_2$)*	$BeCO_3.Be(HO)_2$
Beryllium nitrate	13597-99-4	Beryllium dinitrate; *nitric acid, beryllium salt*	$Be(NO_3)_2$
Beryllium nitrate trihydrate	7787-55-5	*Nitric acid, beryllium salt, trihydrate*	$Be(NO_3)_2.3H_2O$
Beryllium nitrate tetrahydrate	13510-48-0	Beryllium dinitrate tetrahydrate; *nitric acid, beryllium salt, tetrahydrate*	$Be(NO_3)_2.4H_2O$
Beryllium phosphate	13598-15-7	*Phosphoric acid, beryllium salt (1:1)*	$BeHPO_4$
Beryllium silicate[e]	13598-00-0	Phenazite; *phenakite*	$Be_2(SiO_4)$
Zinc beryllium silicate	39413-47-3 (63089-82-7)	*Silicic acid, beryllium zinc salt*	Unspecified

[a] Replaced CAS Registry numbers are shown in parentheses.
[b] Related compound registered by CAS is beryllium alloy, base, Be, Al historically (Lockalloy), Al (24–44%).Be (56–76%) [12604-81-8; replaced Registry No., 12665-28-0]; 60 beryllium–aluminium alloys are registered with CAS numbers, with different percentages of the two elements.
[c] Related compound registered by CAS is beryllium alloy, base, Be,Cu [39348-30-6]; 111 beryllium–copper alloys are registered with CAS numbers, with different percentages of the two elements.
[d] CAS name and Registry number shown were selected as being closest to the formula given byLide (1991). Related compounds registered by CAS are: bis[carbonato(2)]dihydroxytriberyllium, $(BeCO_3)2.Be(OH)_2$ [66104-24-3]; carbonic acid, beryllium salt (1:1), tetrahydrate, $BeCO_3.4H_2O$ [60883-64-9]; carbonic acid, beryllium salt (1:1), $BeCO_3$ [13106-47-3]; and bis[carbonato(2-)]oxodiberyllium, $(CO_3)2Be_2O$ [66104-25-4].
[e] Related compounds registered by CAS are: bertrandite, $Be_4(OH)_2O(SiO_3)_2$ [12161-82-9]; beryllium silicate, formula unspecified [58500-38-2]; silicic acid (H_2SiO_3), beryllium salt (1:1), $Be(SiO_3)$ [14902-94-4]; silicic acid (H_4SiO_4), beryllium salt (1:2), $Be_2(SiO_4)$ [15191-85-2]

the surface of the bare metal, rendering the metal highly resistant to corrosion, to hot and cold water, and to oxidizing acids (Newland, 1984; Petzow *et al.*, 1985; WHO, 1990).

1.3 Use of the agents

Beryllium is primarily used in its metallic form, in alloys, or in beryllium oxide ceramics. Its physical and mechanical properties make it useful for many applications across a range of industries. These properties include: outstanding

strength (when alloyed), high melting-point, high specific heat, excellent thermal properties, electrical conductivity, reflectivity, low neutron absorption, and high neutron-scattering cross-sections, and transparency to X-rays (WHO, 1990; USGS, 2007).

Industries using beryllium and beryllium products include: aerospace (e.g. altimeters, braking systems, engines, and precision tools), automotive (e.g. air-bag sensors, anti-lock brake systems, steering wheel connecting springs), biomedical (e.g. dental crowns, medical laser components, X-ray tube windows), defence (e.g. heat shields, missile guidance systems, nuclear reactor components), energy and electrical (e.g. heat exchanger tubes, microwave devices, relays and switches), fire prevention (e.g. non-sparking tools, sprinkler system springs), consumer products (e.g. camera shutters, computer disk drives, pen clips), manufacturing (e.g. plastic injection moulds), sporting goods (e.g. golf clubs, fishing rods, naturally occurring and man-made gemstones), scrap recovery and recycling, and telecommunications (e.g. mobile telephone components, electronic and electrical connectors, undersea repeater housings) (Kreiss *et al.*, 2007).

1.3.1 Beryllium metal

Some typical applications of beryllium metal include: aerospace technology (structural material, inertia guidance systems, additives in solid propellant rocket fuels, aircraft brakes, mirror components of satellite optical systems, gyroscopes), nuclear technology (moderator and reflector of neutrons in nuclear reactors, neutron source when bombarded with α particles), X-ray and radiation technology (special windows for X-ray tubes), computer technology and alloys (e.g. beryllium–copper alloys; hardening of copper, and developmental brass alloys) (WHO, 1990; Petzow *et al.*, 2007).

1.3.2 Beryllium-containing alloys

Approximately 75% of manufactured beryllium is used in alloys, 95% of which is copper alloy (Jakubowski & Palczynski, 2007). Because of the properties it confers on other metals (i.e. low density combined with strength, high melting-point, resistance to oxidation, and a high modulus of elasticity), beryllium alloys are light-weight materials that can withstand high acceleration and centrifugal forces (WHO, 1990). Beryllium–copper alloys are commonly used in the electronics (e.g. switch and relay blades, electronic connector contacts, control bearings, magnetic sensing device housings, and resistance welding systems), automotive (e.g. air-bag sensors), military (e.g. electro-targeting and infrared countermeasure devices, missile systems, advanced surveillance satellites, and radar systems), and aerospace industries (e.g. landing gear bearings, weather satellites). Other applications include computers, oil exploration equipment, medical appliances, sporting equipment (e.g. golf clubs), and non-sparking tools (e.g. in petroleum refineries) (WHO, 1990; Kaczynski, 2004; Jakubowski & Palczynski, 2007).

1.3.3 Beryllium oxide

The ceramic properties of sintered beryllium oxide make it suitable for the production or protection of materials to be used at high temperatures in corrosive environments. It is used in lasers and electronics (e.g. transistor mountings, semiconductor packages, microelectronic substrates, microwave devices, high-powered laser tubes), in aerospace and military applications (e.g. gyroscopes and armour), refractories (e.g. thermocouple sheaths and crucibles), nuclear technology (reactor fuels and moderators), and medical/dental applications (e.g. ceramic crowns). It is also used as an additive (to glass, ceramics, and plastics) in the preparation of beryllium compounds, and as a catalyst for organic reactions (WHO, 1990; Taylor *et al.*, 2003).

1.3.4 Other beryllium compounds

Other important beryllium compounds include the beryllium halides (beryllium chloride and beryllium fluoride), beryllium hydroxide, and beryllium sulfate. Beryllium chloride has been used as a raw material in the electrolytic production of beryllium, and as the starting material for the synthesis of organo-beryllium compounds (O'Neil, 2006; Petzow *et al.*, 2007). Beryllium fluoride is used as an intermediate in the preparation of beryllium and beryllium alloys. It is used in nuclear reactors and glass manufacture, and as an additive to welding and soldering fluxes (O'Neil, 2006; Petzow *et al.*, 2007). Beryllium hydroxide is used as an intermediate in the manufacture of beryllium and beryllium oxide (O'Neil, 2006). Beryllium sulfate tetrahydrate is used as an intermediate in the production of beryllium oxide powder for ceramics (Kaczynski, 2004).

1.4 Environmental occurrence

Beryllium occurs naturally in the earth's crust, and is released in the environment as a result of both natural and anthropogenic activities. The environmental occurrence of beryllium has been reviewed extensively (WHO, 1990; ATSDR, 2002; Taylor *et al.*, 2003).

1.4.1 Natural occurrence

The 44th most abundant element in the earth's crust, beryllium occurs in rocks and minerals (mica schist, granite, pegmatite, and argillite), although the most highly enriched beryllium deposits are found in granitic pegmatites, in which independent beryllium minerals crystallize. Some 50 beryllium-containing minerals have been identified. Only ores containing beryl ($3BeO.Al_2O_3.6SiO_2$) and bertrandite ($4BeO.2SiO_2.H_2O$) have achieved economic significance. The average terrestrial abundance of beryllium is 2–5.0 mg/kg. (IARC, 1993; Jakubowski & Palczynski, 2007; USGS, 2007).

1.4.2 Air

Beryllium particulates are released in the atmosphere from both natural and anthropogenic sources. Windblown dust is the most important natural source of atmospheric beryllium (approximately 95%), with volcanic activity accounting for the remainder. The major anthropogenic source of atmospheric beryllium is the combustion of coal and fuel oil. Other sources include: municipal waste incineration, beryllium alloy and chemical use (includes ore processing, production, use and recycling), and the burning of solid rocket fuel (WHO, 2001; ATSDR, 2002). Ambient concentrations of atmospheric beryllium are generally low. Based on measurements at 100 locations, an average daily concentration of less than 0.5 ng/m^3 was reported in the United States of America (Jakubowski & Palczynski, 2007). Atmospheric concentrations of beryllium in the vicinity of beryllium-processing plants are often higher than those measured elsewhere (IARC, 1993).

1.4.3 Water

Beryllium is released in the aquatic environment from both natural and anthropogenic sources. Weathering of beryllium-containing rocks and soils is the primary source of release, although leaching of coal piles may also contribute to beryllium entering surface water. Anthropogenic sources include industrial waste water effluents (e.g. from electric utility industries). The deposition of atmospheric fall-out (of anthropogenic and natural sources) is also a source of beryllium in surface waters. However, the relative importance of this contribution to aquatic concentrations of beryllium is difficult to assess (ATSDR, 2002).

Beryllium concentrations in surface waters are usually in the range of 0.01–0.1 µg/L (WHO, 1990). The concentration of beryllium in deep ocean waters tend to be fairly uniform worldwide,

and are estimated to be approximately three orders of magnitude lower than that of surface river water (Jakubowski & Palczynski, 2007). Beryllium concentrations in drinking-water are on average 0.19 µg/L, with a range of 0.01–1.22 µg/L (Kolanz, 2001).

1.5 Human exposure

1.5.1 Exposure of the general population

The primary route of beryllium exposure for the general population is via the ingestion of contaminated food or water. The daily intake of beryllium by non-occupationally exposed persons in the USA from drinking-water is estimated to be 1 µg per day (assuming an average concentration of 0.5 µg/L, and a drinking-water consumption rate of 2 L/day). In the 1980s, the Environmental Protection Agency in the USA estimated the daily intake of beryllium in food to be approximately 0.12 µg per day (based on an arbitrary value of 0.1 ng beryllium per gram of food, and an assumption that a normal adult consumes 1200 g of food per day). Other studies have estimated the daily intake of beryllium in food to be in the range of 5–100 µg per day (ATSDR, 2002).

The inhalation of beryllium via ambient air or smoking is considered to be a minor exposure route for the general population. Assuming an average airborne concentration of less than 0.03 ng/ m^3 beryllium per day, and a breathing rate of 20 m^3 of air per day, the estimated daily intake for an adult in the USA is approximately 0.6 ng of beryllium, or less, per day. This estimated intake is likely to be higher for for persons living near point sources of beryllium emission (ATSDR, 2002).

1.5.2 Occupational exposure

The occupational environment is the predominant source of beryllium exposure for humans. Inhalation of beryllium dust and dermal contact with beryllium-containing products are the main routes of occupational exposure, although there may be the potential for in-home exposure if contaminated work garments are worn at home (ATSDR, 2002; NTP, 2004). Industries using or producing beryllium include: aerospace; automotive; biomedical; defence; energy and electrical; fire prevention; instruments, equipment and objects; manufacturing; sporting goods and jewellery; scrap recovery and recycling; and telecommunications (Kreiss *et al.*, 2007).

Based on data obtained from the primary beryllium industry and government agencies, Henneberger *et al.* (2004) estimated that 134000 workers were potentially exposed to beryllium in the USA (1500 in the primary beryllium industry, 26500 in the Department of Energy or Department of Defence, and between 26400 and 106000 in the private sector, outside of the primary industry). This figure may be an underestimate because of the limited data on potential beryllium exposures in military and nuclear weapons workplaces, and in many others where beryllium is a minor or unsuspected component (e.g. aluminium smelting, scrap recovery, and electronics recycling). The number of workers in the USA ever exposed to beryllium is likely to be far higher than 134000, as it does not include approximately 250000 construction workers that are employed at nuclear weapons reclamation sites alone (Kreiss *et al.*, 2007).

Estimates of the number of workers potentially exposed to beryllium and beryllium compounds have been developed by CAREX in Europe. Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX (CARcinogen EXposure) database estimates that 66069 workers were exposed to beryllium and beryllium compounds in the European Union, with over 80% of workers employed in the manufacture of machinery, except electrical (n = 38543); manufacture of fabricated metal products except machinery and equipment (n = 5434); manufacture of electrical machinery,

apparatus and appliances (*n* = 4174); manufacture of professional, scientific, measuring and controlling equipment not elsewhere classified (*n* = 3708); and manufacture of transport equipment (*n* = 3328). CAREX Canada estimates that 4000 Canadians (86% male) are exposed to beryllium in their workplaces (CAREX Canada, 2011). These industries include: building equipment contractors, medical equipment and supplies manufacturing, residential building construction, motor vehicle parts manufacture, automotive repair and maintenance, non-residential building construction, commercial/industrial machinery repair and maintenance, architectural and structural metals manufacturing.

Data on early occupational exposures to beryllium were summarized in the previous *IARC Monograph* (IARC, 1993), and data from studies on beryllium exposure published since are summarized below.

(a) Processing and manufacturing

Sanderson *et al.* (2001a) investigated historical beryllium exposures in a beryllium-manufacturing plant in the USA during 1935–92 for the purpose of reconstructing exposures for an epidemiological study. Daily weighted average (DWA) exposure estimates ranged from 1.7–767 μg/m^3 for 1935–60; 1.0–69.9 μg/m^3 for 1961–70; 0.1–3.1 μg/m^3 for 1971–80; and 0.03–1.4 μg/m^3 for 1981–92 (range of geometric means).

Seiler *et al.* (1996a, b) investigated historical beryllium exposure data (*n* = 643) collected in five beryllium-processing facilities in the USA during 1950–75. Descriptive data for representative job titles in November 1974 indicated that DWA beryllium exposures ranged from a minimum of 0.3 μg/m^3 for a ceramics machine operator to a maximum of 111.4 μg/m^3 for a vacuum cast furnace operator. Approximately 73% of the maximum breathing zone DWA exposures exceeded the 2 μg/m^3 standard; only 18% of the general air DWA beryllium exposures exceeded the standard.

Deubner *et al.* (2001a) analysed 34307 airborne beryllium measurements (general air, breathing zone, and personal lapel) collected during 1970–99 at a beryllium mining and extraction facility in Delta, UT, USA, and compared them to a mixed beryllium products facility and a beryllium ceramics facility located in Elmore, OH and Tucson, AZ, respectively. DWAs (*n* = 1519) were calculated to estimate task-specific, time-weighted average (TWA) exposures for workers at the Delta facility. The general area and breathing zone sampling data indicated that average annual beryllium concentrations at the Delta plant declined over the study period. The range of annual median general area sample concentrations at the mining and milling plant was comparable to that at the beryllium ceramics facility (0.1–0.6 μg/m^3 versus 0.1–0.4 μg/m^3, respectively). These data were lower than those observed at the mixed beryllium products facility (range of annual median general area sample concentrations, 0.1–1.0 μg/m^3). At the mining and milling facility, the highest exposures were observed in jobs involving beryllium hydrolysis and wet-grinding activities. This observation was independent of the exposure assessment method used.

Kreiss *et al.* (1997) analysed 106218 airborne beryllium measurements collected during 1984–93 at a beryllium-manufacturing plant producing pure metal, oxide, alloys, and ceramics. Of these, 90232 were area samples (30-minute samples: *n* = 30872; full-shift, continuous samples: *n* = 59360), and 15986 were personal samples (1–15 minute breathing zone samples: *n* = 15787; full-shift personal lapel samples: *n* = 179). Using these data, DWA exposures were calculated for most jobs. Median area concentrations were 0.6 μg/m^3 and 0.4 μg/m^3 for full-shift and short-term samples, respectively. Median personal concentrations were 1.4 μg/m^3 and 1.0 μg/m^3 for short-term and full-shift samples, respectively. The highest median area concentrations were observed in the alloy arc furnace

and alloy melting-casting areas, and the highest median breathing zone concentrations were observed in the beryllium powder and laundry areas.

Kent *et al.* (2001) collected full-shift particle-size-specific personal samples (n = 53) and area samples (n = 55) in five furnace areas at a beryllium-manufacturing facility. Personal samples were collected with Anderson impactors and general area samples were collected with micro-orifice uniform deposit impactors (MOUDIs). The median total mass concentration of beryllium particles (in μg/m^3) was reported by work process area and particle size. Median personal aerosol concentrations ranged from 0.8–5.6 μg/m^3 for total particle mass, and 0.05–0.4 μg/m^3 for alveolar-deposited particle mass. Median area concentrations ranged from 0.1–0.3 μg/m^3 for total particle mass, and 0.02–0.06 μg/m^3 for alveolar-deposited particle mass.

(b) Beryllium oxide ceramics

As part of a study to examine the relationship between sensitization and beryllium exposure in a beryllium ceramics plant in the USA, Kreiss *et al.* (1996) reviewed all general area (n = 5664) and personal breathing zone (n = 4208) samples collected during 1981–92. Of the area samples collected, 14% (n = 774) were full-shift samples collected from 1983 onwards; of the personal breathing zone samples, 1.7% (n = 75) were full-shift samples collected from 1991 onwards. Using average general area, full-shift area and breathing zone measurements, DWA exposures for most occupations were calculated. Of the full-shift area samples, 76% were reported to be at or below the detection limit of 0.1 μg/m^3. The median general area concentration was at or below the detection limit, with measured concentrations ranging as high as 488.7 μg/m^3. Median personal breathing zone concentrations were 0.3 μg/m^3 (maximum, 1931 μg/m^3) and 0.20 μg/m^3 (range, 0.1–1.8 μg/m^3) for the short-term and full-shift samples, respectively. Machinists were observed to have the highest exposures, with breathing zone concentrations of 63.7 μg/m^3, and a median DWA exposure of 0.9 μg/m^3.

Henneberger *et al.* (2001) conducted a follow-up to the Kreiss *et al.* (1996) study, screening workers at a US beryllium ceramics plant to determine whether the plant-wide prevalence of beryllium sensitization and disease had declined in the 6-year interval since first screening, and to explore exposure–response relationships. Historical airborne beryllium measurements (task- and time-specific) were combined with individual work histories to compute worker-specific beryllium exposures (mean, cumulative, and peak). A total of 18903 beryllium measurements were collected during 1981–98, of which 43% were short-term (1–15 minute), task-specific personal breathing zone samples, and 57% were short-term (30 minute) general area samples. Mean calculated exposures for all workers ranged from 0.05 μg/m^3 (i.e. less than the limit of detection) to 4.4 μg/m^3. When duration of employment was taken into account, short-term workers (i.e. those hired since the previous survey) had lower mean (median value: 0.28 μg/m^3 versus 0.39 μg/m^3) and peak concentrations (median value: 6.1 μg/m^3 versus 14.9 μg/m^3) than long-term workers.

Cummings *et al.* (2007) conducted a follow-up study in the same beryllium oxide ceramics manufacturing facility considered by Henneberger *et al.* (2001) to assess the effectiveness of an enhanced preventive programme to reduce beryllium sensitization. Sensitization for newly hired workers was compared with that for workers hired from 1993–98, and tested in the 1998 survey. Full-shift personal exposure data collected by the facility from 1994–2003 (n = 1203 measurements) was grouped into two time periods (1994–99 and 2000–03), and three work categories (production, production support, and administration). For the period 1994–99, median beryllium levels were 0.20 μg/m^3, 0.10 μg/m^3, and

less than the limit of detection in production, production support and administration, respectively ($n = 412$, full-shift personal lapel samples). For the later period, median beryllium levels were 0.18 μg/m³, 0.04 μg/m³, and 0.02 μg/m³ in production, production support, and administration, respectively ($n = 791$, full-shift personal lapel samples).

(c) Machining and use

Martyny *et al.* (2000) conducted particle-size selective sampling on five mechanical processes (milling, deburring, lapping, lathe operations, and grinding) to examine the particle size distribution of beryllium machining exposures. Two sets of stationary samples were collected using Lovelace Multijet Cascade Impactors mounted to the machines at 'point of operation' and at 'nearest worker location', two sets of personal samples were collected in the breathing zone of workers operating the machines (one personal pump-powered lapel sampler, one personal cascade impactor), as well as ambient air samples from four fixed locations in the facility. In total, 336 measurements were collected (79 personal pump samples, 87 personal impactor samples, 71 nearest worker location samples, 87 point of operation samples, and 12 ambient air samples. Of these, 243 were samples of the five target processes (64 personal pump samples, 59 personal impactor samples, 64 nearest worker location samples, and 56 point of operation samples). For the stationary area samples, median TWA concentrations were in the range of 0.20 μg/m³ for the 'nearest worker location' samples to 0.60 μg/m³ for the 'point of operation' samples. For the personal breathing zone samples (collected by the personal impactors), median TWA concentrations were in the range of 0.13 μg/m³ for lapping processes to 0.74 μg/m³ for deburring operations. The range of 48-hour median ambient concentration was 0.02–0.07 μg/m³.

To evaluate the effectiveness of a beryllium exposure control programme at an atomic weapons facility in Wales, United Kingdom, Johnson *et al.* (2001) analysed 585438 air monitoring records (367757 area samples collected at 101 locations, and 217681 personal lapel samples collected from 194 workers during 1981–97). Across all departments, the range of annual personal concentrations was 0.11–0.72 μg/m³ (mean) and 0.08–0.28 μg/m³ (median). The highest levels of exposure were observed in foundry workers, with a mean exposure level of 0.87 μg/m³ and a median exposure level of 0.22 μg/m³ (over all years). For the area samples, mean annual concentrations ranged from a high of 0.32 μg/m³ in 1985 to a low of 0.02 μg/m³ in 1997.

(d) Alloy facilities

Schuler *et al.* (2005) analysed airborne beryllium measurements collected in 1969–2000 at a beryllium–copper alloy strip and wire finishing facility. Of the 5989 available measurements, 650 were personal samples, 4524 were general area samples, and 815 were short-duration, high-volume (SD-HV) breathing zone samples. Data were grouped and analysed on the basis of work category (production, production support, administration), and by process or job within each work category. For example, 'rod and wire' production is a subcategory of 'production'; jobs within 'rod and wire' production include: wire annealing and pickling, wire drawing, straightening, point and chamfer, rod and wire packing, die grinding, and, historically, wire rolling. Median plant-wide exposure levels were 0.02 μg/m³ (personal), 0.09 μg/m³ (general area), and 0.44 μg/m³ (SD-HV breathing zone). Among work categories, the highest levels of beryllium exposure were found in 'rod and wire' production (median, 0.06 μg/m³), with the most highly exposed process or job being 'wire annealing and pickling' (median, 0.12 μg/m³).

In a study in a beryllium alloy facility, Day *et al.* (2007) measured levels of beryllium in workplace air ($n = 10$), on work surfaces ($n = 252$), on cotton gloves worn over nitrile gloves ($n = 113$),

and on necks and faces of workers (n = 109). In production, geometric mean levels of beryllium were 0.95 µg/100 cm^2 (work surfaces), 42.8 µg per sample (cotton gloves), 0.07 µg per sample (necks), and 0.07 µg per sample (faces). In production support, geometric mean levels of beryllium were 0.59 µg/100 cm^2 (work surfaces), 73.8 µg per sample (cotton gloves), 0.09 µg per sample (necks), and 0.12 µg per sample (faces). The lowest levels were measured in the administration section, with geometric mean levels of beryllium of 0.05 µg/100 cm^2 (work surfaces), 0.07 µg per sample (cotton gloves), 0.003 µg per sample (necks), and 0.003 µg per sample (faces). Strong correlations were observed between beryllium in air and on work surfaces (r = 0.79), and between beryllium on cotton gloves and on work surfaces (r = 0.86), necks (r = 0.87), and faces (r = 0.86).

Yoshida *et al.* (1997) studied airborne beryllium levels at two beryllium–copper alloy manufacturing factories in Japan during 1992–95. General area samples were collected in the beryllium–copper alloy process (n = 56) and the beryllium–copper metal mould manufacturing process (n = 41) of Factory A, and in the beryllium–copper cold rolling, drawing and heat-treatment process (n = 16) and beryllium–copper slitting treatment process (n = 8) of Factory B. In all years studied, the highest geometric mean beryllium levels were observed in the beryllium–copper alloy process of Factory A (range, 0.16–0.26 µg/m^3).

Stanton *et al.* (2006) studied beryllium exposures among workers at three beryllium–copper alloy distribution centres in the USA in 2000–01. For the period 1996–2004, company records of full-shift personal lapel breathing zone samples for airborne beryllium (n = 393) were examined. A total of 54% of all samples were at or below the limit of detection. The overall median beryllium concentration was 0.03 µg/m^3 (arithmetic mean, 0.05 µg/m^3). When examined by work category (production – bulk products, production – strip metal, production support, administration) and process or job within work category, concentration ranges were 0.01–0.07 µg/m^3 (median), and 0.02–0.07 µg/m^3 (geometric mean). The highest concentrations were measured in heat-treating (bulk products) and tensioning (strip metal) processes, with levels of 1.6 µg/m^3 and 1.4 µg/m^3, respectively.

(e) Nuclear facilities

Stange *et al.* (1996a) studied beryllium exposures in the Rocky Flats Nuclear Facility in the USA. Fixed airhead (i.e. area) samples (n = 102) and personal breathing zone samples (n = 102) were collected from the main beryllium production building. The mean beryllium concentration from the area samples was 0.16 µg/m^3, and from the personal samples, 1.04 µg/m^3. No correlation (r^2 = 0.029) was observed between fixed airhead and personal breathing zone beryllium samples.

Stefaniak *et al.* (2003a) investigated historical beryllium exposure conditions at the Los Alamos Nuclear Laboratory in the USA. A total of 4528 personal breathing zone and area samples were analysed. For all technical areas, the geometric mean concentration for the period 1949–89 was 0.04 µg/m^3. Average beryllium concentrations per decade were less than 1 µg/m^3, and annual geometric mean concentrations in the area that was the largest user of beryllium were generally below 0.1 µg/m^3.

(f) Other

Meeker *et al.* (2006) compared occupational exposures among painters using three alternative blasting abrasives (specular hematite, coal slag, steel grit) on a footbridge painting project during 2002–04 in New Jersey, USA. Over the 3-year project, personal breathing zone samples were collected outside the respirators of two or three abrasive blasters. The range of beryllium concentrations measured outside personal protective equipment (n = 18 samples) was 2.5–9.5 µg/m^3, with a geometric mean exposure

level of 5.0 μg/m³. Beryllium was also measured in bulk paint chips collected from each bridge.

Bauxite, from which aluminium is derived, may contain beryllium in varying degrees. In 965 personal samples collected during 2000–05 in four aluminium smelters, beryllium concentrations varied in the range of 0.002–13.0 μg/m³ (arithmetic and geometric means were 0.22 and 0.05 μg/m³, respectively) (Taiwo *et al.*, 2008).

1.5.3 Dietary exposure

There is a lack of reliable data on the concentration of beryllium in food (WHO, 1990; ATSDR, 2002). Measured concentrations of beryllium have been reported for 38 foods, fruit and fruit juices from around the world (number of samples, 2243; 2209 foods + 34 fruit and juices). Concentrations in the foods have been reported in the range of < 0.1–2200 μg/kg fresh weight, with the highest concentrations measured in kidney beans, crisp bread, garden peas, parsley and pears (2200, 112, 109, 77, and 65 μg/kg fresh weight, respectively), and with a median concentration of 22.5 μg/kg fresh weight (kidney beans were excluded from this calculation). Concentrations in the fruits and juices ranged from not detected to 74.9 μg/L, with an average concentration of 13.0 μg/L (ATSDR, 2002). Beryllium has also been measured in rice, head lettuce, and potatoes at 80 μg/kg, 330 μg/kg, and 0.3 μg/kg, respectively (Kolanz, 2001).

1.5.4 Biomarkers of exposure

Several analytical methods are available and have adequate sensitivity for measuring beryllium in biological samples. These include gas chromatography-electron capture (GC-ECD), graphite furnace atomic absorption spectrometry (GF-AAS), inductively coupled plasma atomic emission spectrometry (ICP-AES), and inductively coupled plasma mass spectrometry (ICP-MS). Biological matrices in which these methods can measure beryllium include: blood, urine, faeces, fingernails, hair, and lung tissue. Urinary beryllium is an indicator of current exposure, but is of uncertain utility for quantitative exposure assessment. Beryllium levels in blood, serum or plasma are indicators of the intensity of current exposure (ATSDR, 2002; NTP, 2004; NRC 2007).

The average burden of beryllium in the general population is 0.20 mg/kg in the lung and is below 0.08 mg/kg in other organs (Kolanz, 2001).

The mean concentration of beryllium in urine measured in about 500 non-occupationally exposed individuals in the USA during the Third National Health and Nutrition Examination Survey (NHANES III) was 0.22 μg/g of creatinine (Paschal *et al.*, 1998). Other studies reported mean urinary beryllium concentrations in the range of < 0.03–0.4 μg/L for non-occupationally exposed individuals (Apostoli & Schaller, 2001).

2. Cancer in Humans

The previous *IARC Monograph* on beryllium and beryllium compounds was based largely on evidence of elevated lung cancer mortality among 689 individuals (predominantly workers) entered into the US Beryllium Case Registry (Steenland & Ward, 1991; Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-02-Table2.1.pdf), and in a cohort of 9225 workers employed at seven beryllium-processing plants in the USA (Ward *et al.*, 1992). The cohort study included two plants that had been previously studied (Mancuso, 1979, 1980; Wagoner *et al.*, 1980) and Infante *et al.* (1980) had reported earlier on mortality in the Beryllium Case Registry cohort.

2.1 Cohort studies and nested case–control studies

The body of evidence available for the current evaluation of the carcinogenicity of beryllium in humans includes the two previously evaluated cohort studies and a nested case–control study initially reported by Sanderson *et al.* (2001b), and reanalysed with adjustment for temporal confounders by Schubauer-Berigan *et al.* (2008).

The Beryllium Case Registry study included 689 individuals entered alive into the registry and followed for mortality through to 1988 (Steenland & Ward, 1991); 34% were from the fluorescent tube industry, and 36% were from basic manufacturing. There were 158 deaths from pneumoconiosis and other respiratory disease, the category that included beryllium disease (Standard Mortality Ratio [SMR], 34.2; 95%CI: 29.1–40.0). The overall SMR for lung cancer was 2.00 (95%CI: 1.33–2.89), based on 28 deaths. Among those with acute beryllium disease, there were 17 lung cancer deaths (SMR 2.32; 95%CI: 1.35–3.72), and among those with chronic beryllium disease, ten lung cancer deaths (SMR 1.57; 95%CI: 0.75–2.89).

The cohort study included workers at seven beryllium-processing plants in the USA involved in various phases of beryllium processing with exposure to many forms of beryllium and beryllium compounds (Ward *et al.*, 1992). The study found a significantly elevated SMR of 1.26 (95%CI: 1.12–1.42) for lung cancer in the cohort overall, with significant excesses observed for the two oldest plants located in Lorain, Ohio, and Reading, Pennsylvania.

The SMR for lung cancer at the Lorain plant was 1.69 (95%CI: 1.28–2.19), and at the Reading plant, 1.24 (95%CI: 1.03–1.48). The Lorain plant, in operation during 1935–48, is thought to have had very high beryllium exposures. The majority of workers (84.6%) were employed for less than 1 year. Ninety-eight of the 1192 individuals employed at the Lorain plant (8.2%) were identified in the Beryllium Case Registry as having beryllium disease; 91 were of the acute form which has only been associated with very high beryllium exposure, six individuals had chronic beryllium disease, and one was of unknown type. A total of 11 lung cancer deaths occurred among the 98 individuals with beryllium disease (SMR, 3.33; 95%CI: 1.66–5.95), and 46 lung cancer deaths occurred among the remaining 1094 Lorain workers (SMR, 1.51; 95%CI: 1.11–2.02). All but one of the 57 lung cancer deaths occurred in latency categories < 15 years; for 15–30 years' latency, the SMR was 2.09 [95%CI: 1.30–3.21]; and for over 30 years' latency, 1.66 [95%CI: 1.16–2.31].

The plant in Reading, Pennsylvania, in operation during 1935–2001, employed 3569 workers during 1940–69. Among those, 53.8% were employed for less than 1 year, and only 17.2% were employed for more than 10 years. When the SMRs for lung cancer at the Reading plant were analysed by latency and duration of exposure, the highest SMR was observed for the category with less than 1 year of employment and duration and more than 30 years' latency (SMR = 1.42; [95%CI: 1.01–1.93]). Further analyses by decade of hire revealed that 92/120 lung cancer deaths occurred among workers hired before 1950 (SMR, 1.26; [95%CI: 1.02–1.55]). None of the newer plants included in the study had a significantly elevated SMR for lung cancer. However, non-significantly elevated SMRs were observed for four out of five plants operating in the 1950s for workers hired during that decade. The results were adjusted for smoking based on comparing smoking histories of 1466 (15.9%) of cohort members surveyed in 1968 with a survey of the US population conducted in 1965, resulting in SMRs of 1.12, 1.49 and 1.09 for the total cohort, the Lorain plant, and the Reading plant, respectively. [The Working Group noted that it is unclear that adjustment for differences in smoking patterns between cohort members and the US population in the late 1960s would accurately reflect patterns

in the 1940s that would be most relevant to interpreting the lung cancer excess. It is possible that using data from the 1960s would overestimate the impact of smoking.] SMRs based on county referent rates were also presented and for the cohort as a whole, the SMR was slightly increased to 1.32, the SMR declined for the Lorain plant to 1.60, and increased for the Reading plant to 1.42.

Subsequent to the publication of the Ward *et al.* (1992) study, the Beryllium Industry Scientific Advisory Committee suggested that the excess of lung cancer observed at the Lorain plant might be attributable to exposure to sulfuric acid mist and fumes rather than exposure to beryllium (BISAC, 1997). A reanalysis of the cohort study used alternative referent rates (for cities in which the two oldest plants were located) to compute expected number of lung cancers, alternative smoking risk factor estimates to adjust for differences in smoking habits between the cohort and the US population, and an alternative methodology to calculate the SMR for all plants combined (Levy *et al.*, 2002). The net effect of the reanalysis was to reduce the magnitude and statistical significance of the SMRs in the Ward *et al.* (1992) study. [The Working Group noted that there are several potential methodological limitations of this reanalysis. For instance, the city referent rates used for the calculation were not published, whereas Ward *et al.* (1992) used only published rates.]

Sanderson *et al.* (2001b) conducted a nested case–control study of lung cancer within one of the beryllium processing plants studied by Ward *et al.* (1992). This plant was selected for study because it was one of the two older plants in which an elevated lung cancer SMR was observed, and because industrial hygiene measurement data were available from as early as 1947. Details of the job–exposure matrix are provided in Sanderson *et al.* (2001a). Mortality was followed-up through 1992, and 142 lung cancer cases were identified. Cases were age- and race-matched to five controls through incidence-density sampling (Sanderson *et al.*, 2001b). The main findings of the Sanderson *et al.* (2001b) study were positive associations with average and maximum exposure lagged 10 and 20 years. This association did not appear to be confounded by smoking in an analysis that excluded professional workers.

Following some letters and critiques of the Sanderson *et al.* (2001b) study (Deubner *et al.*, 2001b, 2007; Sanderson *et al.*, 2001c; Levy, *et al.*, 2007), a reanalysis of the study was carried out that adjusted for year of birth and an alternative minimal exposure value (the lowest detectable exposure level divided by two) in continuous exposure–response analyses (Schubauer-Berigan *et al.*, 2008; see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-02-Table2.2.pdf). After controlling for year of birth, significantly elevated odds ratios for 10-year lagged average beryllium exposure were found in the middle two exposure quartiles. The choice of an alternative minimal exposure value decreased the trend statistic for cumulative exposure but increased it for average exposure. In the continuous analysis of average 10-year lag dose, the parameter estimates and *P*-values were highly significant with control for year of birth. [The Working Group noted that several methodological articles were published regarding the incidence-density sampling methods used in the nested case–control study (Deubner & Roth, 2009; Hein *et al.*, 2009; Langholz & Richardson, 2009; Wacholder, 2009). Three of these articles affirmed the methodology used to select controls in the study (Hein *et al.*, 2009; Langholz & Richardson, 2009; Wacholder, 2009). The Working Group noted that the issues raised in the Deubner & Roth (2009) commentary did not undermine confidence in the results of the Schubauer-Berigan *et al.* (2008) reanalysis.]

2.2 Synthesis

A large body of evidence was evaluated by the Working Group and, in conclusion, elevated lung cancer mortality was observed in a study of individuals with beryllium disease and in a cohort study of workers at seven beryllium-processing plants. The association of the elevated lung cancer risks with beryllium exposure is supported by a large number of lung cancer cases and stable rate ratios, a consistency in findings among plants, higher risks of lung cancer among workers hired before 1950 (when exposures were at their highest), a greater risk of lung cancer in the US Beryllium Case Registry cohort (especially among those highly exposed who were diagnosed with acute pneumonitis), and greatest risks for lung cancer in the plants with the highest risk for acute pneumonitis and other respiratory disease. In addition, the nested case–control studies found evidence for an exposure–response relationship that was strongest when using the 10-year lag average-exposure metric. All of the epidemiological studies involved potential exposure to metallic beryllium as well as other beryllium compounds, and were unable to discern the specific effects of beryllium metal or specific beryllium compounds.

3. Cancer in Experimental Animals

Beryllium compounds have been tested for carcinogenicity by inhalation in rats and mice, by intratracheal or intrabronchial administration in rats, by intravenous administration to rabbits, by intraperitoneally administration to mice, and by intramedullary bone administration in rabbits.

To date, by all routes of exposure and in all species tested, all beryllium compounds examined have been shown to be carcinogenic (IARC, 1993).

3.1 Inhalation exposure

3.1.1 Mouse

In p53 heterozygous mice, lung tumours occurred after a single series of three consecutive daily inhalation exposures to beryllium metal (Finch *et al.*, 1998a).

3.1.2 Rat

The first inhalation study published on beryllium was with beryllium sulfate in rats, which induced lung tumours and chronic lung disease (Schepers *et al.*, 1957). Inhalation of single doses of beryllium metal (Nickell-Brady *et al.*, 1994), and exposure to beryllium sulfate for 6 months (Schepers *et al.*, 1957) or 72 weeks (Reeves *et al.*, 1967) caused lung tumours in rats. Beryl ore dust induced lung tumours in rats (Wagner *et al.*, 1969).

3.1.3 Hamster

A study of inhalation of beryl ore for 17 months in hamsters resulted in excess atypical lung proliferative lesions, some of which described as tumours (Wagner *et al.*, 1969). It is noteworthy that similar doses caused tumours in rats (Wagner *et al.*, 1969).

See Table 3.1.

3.2 Intratracheal administration

3.2.1 Rat

A single intratracheal administration of beryllium metal, beryllium oxide, and beryllium hydroxide once per week for 15 weeks caused lung tumours in rats (Groth *et al.*, 1980). Beryllium oxide caused lung tumours in rats (Ishinishi *et al.*, 1980; Litvinov *et al.*, 1983).

See Table 3.2.

Table 3.1 Studies of cancer in experimental animals exposed to beryllium (inhalation exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, p53 Heterozygous (M, F) 6–19 mo Finch *et al.* (1998a)	Beryllium metal Single exposure to 47 µg or 3×/d 63 µg 15/group/sex	Lung (tumours, both sexes combined): P53–controls 0/30, low dose 0/29, high dose 4/28 (14%) Wild-type–0/28	$P = 0.048$	
Rat, Wistar and Sherman (M, F) 18 mo (22 mo for controls) Schepers *et al.* (1957)	Beryllium sulfate tetrahydrate Inhalation 35.8 µg/m³ 5.5 d/wk during 180 d 84, 139 controls	Lung (tumours): 76 in 52 rats that survived after exposure period Controls–0/139	NR	Incomplete reporting of the study, total tumours not incidence reported, disease outbreak killed 58 rats during exposure and afterwards, data not divided up by strain or sex
Rat, SD CD rats (M, F) 72 wk Reeves *et al.* (1967)	Beryllium sulfate tetrahydrate Inhalation 34.25 µg/m³ 7 h/d, 5 d/wk, 150/group	Lung (pulmonary alveolar adenocarcinomas, multiple): 43/43 (100%) rats alive past 13 mo Controls–none	NR	Age at start, 6 wk Incomplete reporting of the study, respiratory infections, dead rats thrown out due to postmortem changes
Rat, Charles River CD (M) For each ore – up to 23 mo Wagner et al. (1969)	Beryl ore or bertrandite ore Inhalation 15mg/m³, 6 h/d, 5 d/wk (210–620 µg/m³ beryllium) 93, 33 controls	*Beryl* Lung: **12 mo** 5/11 (45%) squamous metaplasias or small epidermoid tumours **17 mo** 18/19 (95%) lung tumours (alveolar cell tumours–7 adenomas, 9 adenocarcinomas, 4 epidermoid tumours) *Bertrandite* None Controls, none	NR	High crystalline silica content of bertrandite ore Incomplete reporting of the study

Table 3.1 (continued)

Species, strain (sex) **Duration** **Reference**	**Dosing regimen** **Animals/group at start**	**Incidence of tumours**	**Significance**	**Comments**
Hamster, Syrian golden (M) 17 mo Wagner *et al.* (1969)	Beryl ore or bertrandite ore Inhalation 15 mg/m^3, 6 h/d, 5 d/wk 48/group	*Both ores* **12 mo** Atypical lung proliferations **17 mo** More atypical lesions in beryl-exposed hamsters No definitive tumours	NR	Incomplete reporting of the study, lung lesions called adenomas in the figure only, but were probably adenomatous hyperplasias, and not tumours
Rats, F344 (M, F) 14 mo Nickell-Brady *et al.* (1994)	Beryllium metal Inhalation (nose-only) Single exposure 40, 110, 360 and 430 µg (cohort of Lovelace High dose study) 30/group/sex	Lung (tumours): 64% Controls, NR		Age at start, 12 wk No incidence data by group or sex

d, day or days; F, female; h, hour or hours; M, male; mo, month or months; NR, not reported; wk, week or weeks

Table 3.2 Studies of cancer in experimental animals exposed to beryllium (intratracheal or intrabronchial exposure)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar (F) 18 mo Groth *et al.* (1980)	Intratracheal single exposure to 0.5 or 2.5 mg beryllium metal or beryllium–aluminum alloy, beryllium–copper alloy, beryllium–copper–cobalt alloy, beryllium–nickel alloy 35/group	Lung (adenomas or carcinomas): Beryllium metal– 2/3 (67%) low dose, 6/6 (100%) high dose Passivated beryllium metal– 7/11 (64%) low dose, 4/4 (100%) high dose Alloy groups– all negative Controls, 0/21 after 19 mo Beryllium hydroxide– 13/25 (52%) adenoma or adenocarcinoma	$P < 0.008$	Age at start, 3 mo Low beryllium content of alloys Incidence of animals sacrificed at 19 mo reported
Rat, Wistar (F) 19 mo Groth *et al.* (1980)	Intratracheal 50 µg beryllium hydroxide initially followed by 25 µg 10 mo later 35/group	Lung (tumours): 13/25 (52%); Controls, 0/21	$P = 0.0021$	Incidence in rats surviving 16 mo or more
Rat, Wistar (M) Life span Ishinishi *et al.* (1980)	Intratracheal instillation 1 mg beryllium oxide once/wk for 15 wk 30; 16 controls	Lung (tumours): 6/30 (20%, 4 benign, 2 malignant) Controls, 0/16		Animals/group at start NR Untreated controls, 3/4 adenomas have histology indicative of malignancy
Rat, albino (NR) Life span Litvinov *et al.* (1983)	Intratracheal Single exposure beryllium oxide, low- and high-temp fired 0.036, 0.36, 3.6, 18 mg/kg 300 controls	Lung (tumours, malignant): High temp fired– 0/76, 0/84, 2/77 (3%), 2/103 (2%) Low temp fired– 3/69 (4%), 7/81 (9%), 18/79 (23%), 8/26 (31%) Controls, 0/104	NR	

d, day or days; F, female; h, hour or hours; M, male; mo, month or months; NR, not reported; wk, week or weeks

3.3 Intravenous administration

3.3.1 Mouse

A mouse study reported bone tumours after intravenous injection of zinc beryllium silicate (Cloudman *et al.*, 1949).

3.3.2 Rabbit

Multiple intravenous injections of beryllium metal (Barnes & Denz, 1950), beryllium oxide (Gardner & Heslington, 1946; Dutra & Largent, 1950; Araki *et al.*, 1954; Komitowski, 1967; Fodor, 1977), beryllium silicate, beryllium phosphate (Araki *et al.*, 1954), and zinc beryllium silicate (Gardner & Heslington, 1946; Cloudman *et al.*, 1949; Barnes & Denz, 1950; Hoagland *et al.*, 1950; Janes *et al.*, 1954; Kelly *et al.*, 1961) caused osteosarcomas in rabbits, which were reviewed by Groth (1980).

See Table 3.3.

[The Working Group noted that although many of these studies had defficiency in reporting methods, the rarity of the induced tumours was considered to be compelling enough to consider them as a group.]

3.4 Other routes of exposure

3.4.1 Mouse

Beryllium sulfate injected intraperitoneally caused an increased incidence and multiplicity of lung tumours in A/J mice (Ashby *et al.*, 1990).

3.4.2 Rabbit

Intramedullary bone administration of beryllium oxide (Yamaguchi, 1963; Komitowski, 1974; Hiruma, 1991), beryllium silicate (Tapp, 1966), zinc beryllium silicate (Tapp, 1969; Mazabraud, 1975), beryllium carbonate (Matsuura, 1974), and beryllium acetylacetonate (Matsuura, 1974) caused osteosarcomas or other bone tumours in rabbits.

See Table 3.4.

3.5 Synthesis

Lung tumours were induced in rats by inhalation of beryllium sulfate, beryllium metal, and beryl ore dust. In mice, lung cancer occurred after inhalation of beryllium metal. In hamsters, inhalation of beryl ore induced adenomatous hyperplasia of the lung. Intratracheal instillation of beryllium metal, beryllium hydroxide, and beryllium oxide in rats induced lung tumours. Intraperitoneal injection of beryllium sulfate induced lung tumours in mice. Intravenous injection or intramedullary injection/implantation of various beryllium compounds induced osteosarcoma in various studies in rabbits, and in one study in mice.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

The bioavailability of beryllium particles as a function of size (geometric mean diameter), chemical composition, and specific surface area has been studied extensively. The agglomeration of beryllium particles does occur but the agglomerates dissociate again in fluid, with a corresponding decrease in particle mean diameter (Kent *et al.*, 2001; Stefaniak *et al.*, 2003b, 2004, 2007). Highly significant associations of chronic beryllium disease (CBD) and beryllium sensitization with particle-mass concentration for particles of less than 10 µm have been observed. The particle-mass concentration of alveolar-deposited particles (< 10 µm) correlates significantly with the occurrence of CBD. In a simulated phagolysosomal fluid, dissolution rate constants (k) for metallic beryllium particles and multiconstituent particles from arc-furnace processing of a beryllium–copper alloy were greater than those observed for beryllium oxide materials (Stefaniak *et al.*, 2006). Beryllium has

Table 3.3 Studies of cancer in experimental animals exposed to beryllium (intravenous exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse Strain, sex and duration, NR Cloudman *et al.* (1949)	Zinc beryllium silicate (0.264 mg Be); beryllium oxide (1.54 mg Be) 20–22 injections (twice weekly) Number at start, NR	"Some mice" developed malignant bone tumours		Animals/group at start NR Only zinc beryllium silicate induced osteosarcomas
Rabbit Strain, sex and duration, NR Barnes & Denz (1950)	Beryllium metal Total dose, 40mg 24 animals	Bone (sarcomas): 2 surviving rabbits		Toxicity in 19 rabbits during first wk and mo (liver necrosis)
Rabbit Strain and sex, NR > 7 mo Gardner & Heslington (1946)	Zinc beryllium silicate and beryllium oxide 20 doses, total dose–1 g of particles 7 animals	Osteosarcomas: *Zinc beryllium silicate–* 7/7 (100%) that lived past 7 mo *Beryllium oxide–* 1		
Rabbit Strain and sex, NR > 1 yr Cloudman *et al.* (1949)	Zinc beryllium silicate (17 mg Be) or beryllium oxide (390 mg Be) 20–22 injections (twice weekly)	Bone (tumours): *Zinc beryllium silicate–* 4/5 (80%)		Animals/group at start NR
Rabbit Strain, NR (M, F) > 30 wk Barnes & Denz (1950)	Zinc beryllium silicate or beryllium silicate 6–10 injections 67 animals	Bone (sarcomas): *Zinc beryllium silicate–* 7/21 (33%) past 30 wk		Poor survival
Rabbit Strain, NR (M, F) > 11.5 mo Dutra & Largent (1950)	Beryllium oxide or calcined phosphor with beryllium oxide, zinc oxide and silica 20–26 injections 360–700 mg beryllium in beryllium oxide 64–90 mg beryllium in phosphor group	Osteosarcomas: *Beryllium oxide–* 6/6 (100%) *Phosphor–* 2/3 (67%) Controls, 0/50		Animals/group at start NR
Rabbit Strain, NR (M, F) 14–28 mo Hoagland *et al.* (1950)	Beryllium phosphate Zinc beryllium silicate Beryllium oxide 1–4-d intervals, unknown time period Doses not clear 24 animals	Osteosarcomas: *Zinc beryllium silicate–* 7/8 (88%) *Beryllium oxide–* 1		Small group size, lack of controls Incomplete reporting

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rabbit Strain and sex, NR 18 mo Araki *et al.* (1954)	Beryllium phosphate 1 g Beryllium oxide 1 g Beryllium oxide + zinc oxide Single dose 35 animals	Osteosarcomas: *Beryllium phosphate–* 2/4 (50%) *Beryllium oxide+zinc oxide–* 9/31 (29%)		Weight ≈2.0 kg Small numbers of animals, no appropriate controls
Rabbit (M) Strain, NR Janes *et al.* (1954)	Zinc beryllium silicate (1 g beryllium silicate, 33.6 mg beryllium oxide) Twice/wk for 10 wk 10 animals	Osteosarcomas: 5		Age at start, 9–11 mo Small group size, lack of controls
Rabbit Strain and sex, NR 57 wk Kelly *et al.* (1961)	Zinc beryllium silicate Twice/wk for 10 wk 14 animals	Osteosarcomas: 10/14 (71%)		Small group size, lack of controls
Rabbit Strain and sex, NR 15–18 mo Komitowski (1967)	Beryllium oxide Single 1 g dose 20 animals	Osteosarcomas: 3/20 (15%)		Lack of appropriate control group
Rabbit Strain and sex, NR 25 wk Fodor (1977)	Beryllium oxide (1%) Once/wk for 25 wk 60 animals	Sarcomas: 21/29 (72%)		Age at start, 6 mo Incomplete reporting, lack of appropriate control group

d, day or days; F, female; M, male; mo, month or months; NR, not reported; wk, week or weeks

Table 3.4 Studies of cancer in experimental animals exposed to beryllium (other routes of exposure)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, A/J (M) 32 wk Ashby *et al.* (1990)	Intraperitoneal Beryllium sulfate tetrahydrate 0, 0.02, 0.05, 0.1 mg/mouse/injection 3×/wk for 8 wk 20/group	Incidence (% given only): 15, 17, 33, 38% Lung tumours/mouse: 0.15, 0.17, 0.39, 0.38	r = 5.9 and 4.6 for middle and high doses (χ^2)	Age at start, 5–6 wk Purity, 99% Middle and high doses, significant
Rabbit Strain and sex, NR 1–2 yr Yamaguchi (1963)	Injection into bone marrow Beryllium oxide 10 mg twice/wk 55 animals	Bone (tumours): 26		
Rabbit, mixed breeds (M, F) 15–20 mo Tapp (1966)	Intramedullary injection Beryllium silicate powder 20 mg 12 animals	Osteogenic sarcomas: 4/12 (33%)		Age at start, 6 wk
Rabbit, mixed breeds (M, F) 25 mo Tapp (1969)	Implants (periosteal) Zinc beryllium silicate, beryllium oxide, beryllium silicate 10 mg 18 animals	Osteogenic sarcomas: 4/18 (22%)		Age at start, 6 and 8 wk
Rabbit Strain and sex, NR 24 mo Komitowski (1974)	Intramedullary injection Beryllium oxide No dose given 20 animals	Osteogenic sarcomas: 5/20 (25%)		Incomplete reporting, lack of appropriate control group
Rabbit Strain and sex, NR 21 mo Matsuura (1974)	Intramedullary implants Beryllium carbonate, beryllium acetate, beryllium acetylacetonate, beryllium laurate, beryllium stearate 173, 18, 3, 3	Osteosarcomas: *Beryllium carbonate*– 30 *Beryllium acetylacetonate*– 1		Incomplete reporting, small numbers in most groups
Rabbit, Fauve de Bourgogne, sex (NR) > 4 mo Mazabraud (1975)	Intraosseous injection Zinc beryllium silicate 1 g/cm^3 65 animals	Osteogenic sarcomas: 45/65 (69%)		Age at start, 15–20 wk Incomplete reporting Lack of appropriate control group
Rabbit (M) 56 wk Hiruma (1991)	Implants into bone Beryllium oxide 300 (after fracture), 300, 50 mg 10/group	Osteosarcomas: 10/10 (100%) 7/10 (70%) 1/10 (10%)		

F, female; M, male; mo, month or months; NR, not reported; wk, week or weeks; yr, year or years

been detected in CBD-associated granulomas of beryllium-exposed workers by secondary ion mass-spectroscopy at an average of 9 years post exposure (Sawyer *et al.*, 2005a). These data indicate that beryllium is retained in granulomatous lesions for extended periods of time in exposed humans with CBD. Verma *et al.*, (2003) also reported elevated concentrations of beryllium in lung tissue from a person with CBD.

Acute inhalation dose–response studies in mice with a follow-up period of 350 days showed that high-dose exposures produced granulomatous beryllium lesions, which impeded the clearance of beryllium from the lungs (Finch *et al.*, 1998b).

Accidental exposure of 25 people to beryllium dust produced a mean serum concentration of 3.5 μ/L measured one day later, which decreased to a mean concentration of 2.4 μ/L after 6 days (Zorn *et al.*, 1986). These data indicate that beryllium from beryllium metal is biologically available from the lung. Exposure to beryllium metal (Williams, 1977) and beryllium alloys (Lieben *et al.*, 1964) have been reported to produce beryllium disease.

4.2 Genetic and related effects

4.2.1 Direct genotoxicity

A large number of mutagenicity studies for beryllium compounds have been published (for reviews see IARC, 1993; Gordon & Bowser, 2003). In general, results of these studies have been either negative or weakly positive, depending on the test system used.

Joseph *et al.* (2001) studied gene expression patterns in BALB/c-3T3 cells transformed with beryllium sulfate and reported a general upregulation of several cancer-related genes. Because no toxicity data were provided in these studies, the relevance of these findings to cancer cannot be interpreted. The same authors also reported the downregulation of several genes involved in DNA synthesis, repair and recombination in the tumour cells relative to controls.

Fahmy *et al.* (2008) studied the genotoxicity of beryllium chloride in mice exposed to oral doses of 93.75–750 mg/kg body weight for 3 weeks. Starting with the second lowest concentration (187.5 mg/kg bw; 1/8 of the LD_{50}), chromosomal aberrations (excluding gaps) and aneuploidy were observed both in bone-marrow cells and in spermatocytes, as a function of dose and time.

4.2.2 Indirect effects related to genotoxicity

(a) Oxidative stress

Palmer *et al.* (2008) demonstrated upregulation of the protein PD-1 (programmed death-1) in beryllium-specific CD4+ T-cells derived from broncho-alveolar lavages from beryllium-sensitized persons or CBD patients. Upregulation of PD-1 was closely correlated with the severity of T-cell alveolitis.

Subsequent studies by Sawyer *et al.* (2005b) in mouse macrophages demonstrated beryllium-induced formation of reactive oxygen species *in vitro*, with marked increases in apoptosis and activation of caspase 8. These effects were attenuated by the addition of the antioxidant manganese(III)*meso*-tetrakis(4-benzoic acid) porphyrin (MnTBAP).

The inflammatory processes associated with the development of acute or chronic beryllium disease could plausibly contribute to the development of lung cancer by elevating the rate of cell turnover, by enhancing oxidative stress, and by altering several signalling pathways involved in cell replication.

(b) Epigenetic mechanisms

Studies by Belinsky *et al.* (2002) in beryllium-induced rat lung tumours demonstrated hypermethylation of the *p16* and *estrogen-receptor-α* genes, and their attendant inactivation.

4.3 Synthesis

Several molecular mechanisms, possibly interrelated, operate in beryllium-induced carcinogenesis. Whereas mutagenicity tests with beryllium have shown only weakly positive or negative results, chromosomal aberrations and aneuploidy were observed *in vivo* in mice, at non-toxic concentrations. Like many other carcinogenic metals, beryllium is capable of producing oxidative stress, which can lead to cell injury in the form of DNA damage, activation of proto-oncogenes, and apoptotic mechanisms. In addition, the toxicity of beryllium in the lung may lead to cell killing and compensatory cell proliferation. Furthermore, the beryllium-induced chronic inflammatory response with attendant release of cytokines from beryllium-reactive CD4+ T-cells could also play a role in the development of a carcinogenic response in lung tissue.

In addition to beryllium-mediated generation of reactive oxygen species, inflammatory processes induced by beryllium may also cause an increase in reactive oxygen species, mediate cell turnover, and alter cell-signalling pathways. Furthermore, downregulation of genes involved in DNA synthesis, repair and recombination also occurs. Thus, the processes underlying beryllium-induced carcinogenesis are clearly complex, with several possible interactive mechanisms.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of beryllium and beryllium compounds. Beryllium and beryllium compounds cause cancer of the lung.

There is *sufficient evidence* in experimental animals for the carcinogenicity of beryllium and beryllium compounds.

Beryllium and beryllium compounds are *carcinogenic to humans (Group 1).*

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CADMIUM AND CADMIUM COMPOUNDS

Cadmium and cadmium compounds were considered by previous IARC Working Groups in 1972, 1975, 1987, and 1993 (IARC, 1973, 1976, 1987, 1993a). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Synonyms, trade names and molecular formulae for cadmium, cadmium–copper alloy, and some cadmium compounds are presented in Table 1.1. The cadmium compounds shown are those for which data on carcinogenicity or mutagenicity were available or which are commercially important compounds. It is not an exhaustive list, and does not necessarily include all of the most commercially important cadmium-containing substances.

1.2 Chemical and physical properties of the agents

Cadmium (atomic number, 48; relative atomic mass, 112.41) is a metal, which belongs to group IIB of the periodic table. The oxidation state of almost all cadmium compounds is +2, although a few compounds have been reported in which it is +1. Selected chemical and physical properties of cadmium compounds are presented in the previous *IARC Monograph* (IARC, 1993a).

1.3 Use of the agents

Cadmium metal has specific properties that make it suitable for a wide variety of industrial applications. These include: excellent corrosion resistance, low melting temperature, high ductility, high thermal and electrical conductivity (National Resources Canada, 2007). It is used and traded globally as a metal and as a component in six classes of products, where it imparts distinct performance advantages. According to the US Geological Survey, the principal uses of cadmium in 2007 were: nickel–cadmium (Ni–Cd) batteries, 83%; pigments, 8%; coatings and plating, 7%; stabilizers for plastics, 1.2%; and other (includes non-ferrous alloys, semiconductors and photovoltaic devices), 0.8% (USGS, 2008).

Cadmium is also present as an impurity in non-ferrous metals (zinc, lead, and copper), iron and steel, fossil fuels (coal, oil, gas, peat, and wood), cement, and phosphate fertilizers. In these products, the presence of cadmium generally does not affect performance; rather, it is regarded as an environmental concern (International Cadmium Association, 2011). Cadmium is also produced from recycled materials (such as Ni–Cd batteries and manufacturing scrap) and some

Table 1.1 Chemical names, synonyms (CAS names are in italics), and molecular formulae of cadmium and cadmium compounds

Chemical name	CAS Reg. No.[a]	Synonyms	Formula
Cadmium	7440-43-9	Cadmium metal	Cd
Cadmium acetate	543-90-8 (24 558-49-4; 29 398-76-3)	*Acetic acid, cadmium salt*; bis(acetoxy)-cadmium; cadmium (II) acetate; cadmium diacetate; cadmium ethanoate	$Cd(CH_3COO)_2$
Cadmium carbonate	513-78-0 [93820-02-1]	*Carbonic acid, cadmium salt*; cadmium carbonate ($CdCo_3$); cadmium monocarbonate	$CdCO_3$
Cadmium chloride	10 108-64-2	Cadmium dichloride; dichlorocadmium	$CdCl_2$
Cadmium hydroxide	21 041-95-2 (1 306-13-4; 13 589-17-8)	*Cadmium hydroxide ($Cd(OH)_2$)*; cadmium dihydroxide	$Cd(OH)_2$
Cadmium nitrate	10 325-94-7 (14 177-24-3)	*Nitric acid, cadmium salt*; cadmium dinitrate; cadmium (II) nitrate	$Cd(NO_3)_2$
Cadmium stearate	2223-93-0	Cadmium distearate; cadmium octadecanoate; cadmium(II) stearate; octadecanoic acid, cadmium salt; *stearic acid, cadmium salt*	$Cd(C_{36}H_{72}O_4)$
Cadmium sulfate	10 124-36-4 (62 642-07-3) [31119-53-6]	Cadmium monosulfate; cadmium sulfate; *sulfuric acid, cadmium salt (1:1)*	$CdSO_4$
Cadmium sulfide	1306-23-6 (106 496-20-2)	Cadmium monosulfide; cadmium orange; cadmium yellow	CdS
Cadmium oxide	1306-19-0	Cadmium monoxide	CdO
Cadmium–copper alloy[b]	37 364-06-0	*Copper base, Cu, Cd*	Cd.Cu
	12 685-29-9 (52 863-93-1)	*Cadmium nonbase, Cd, Cu*	
	132 295-56-8	*Copper alloy, base, Cu 99.75–100, Cd 0.05–0.15*; UNS C14300	
	132 295-57-9	*Copper alloy, base, Cu 99.60–100, Cd 0.1–0.3*; UNS C14310	

[a] Replaced CAS Registry numbers are shown in parentheses; alternative CAS Registry numbers are shown in brackets.
[b] Sample of cadmium–copper alloys registered with the Chemical Abstracts Service

residues (e.g. cadmium-containing dust from electric arc furnaces) or intermediate products. Recycling accounts for approximately 10–15% of the production of cadmium in developed countries (National Resources Canada, 2007).

The primary use of cadmium, in the form of cadmium hydroxide, is in electrodes for Ni–Cd batteries. Because of their performance characteristics (e.g. high cycle lives, excellent low- and high-temperature performance), Ni–Cd batteries are used extensively in the railroad and aircraft industry (for starting and emergency power), and in consumer products (e.g. cordless power tools, cellular telephones, camcorders, portable computers, portable household appliances and toys) (ATSDR, 2008; USGS, 2008).

Cadmium sulfide compounds (e.g. cadmium sulfide, cadmium sulfoselenide, and cadmium lithopone) are used as pigments in a wide variety of applications, including engineering plastics, glass, glazes, ceramics, rubber, enamels, artists colours, and fireworks. Ranging in colour from yellow to deep-red maroon, cadmium pigments have good covering power, and are highly resistant to a wide range of atmospheric and environmental conditions (e.g. the presence of hydrogen

sulfide or sulfur dioxide, light, high temperature and pressure) (Herron, 2001; ATSDR, 2008; International Cadmium Association, 2011).

Cadmium and cadmium alloys are used as engineered or electroplated coatings on iron, steel, aluminium, and other non-ferrous metals. They are particularly suitable for industrial applications requiring a high degree of safety or durability (e.g. aerospace industry, industrial fasteners, electrical parts, automotive systems, military equipment, and marine/offshore installations) because they demonstrate good corrosion resistance in alkaline or salt solutions, have a low coefficient of friction and good conductive properties, and are readily solderable (UNEP, 2008; International Cadmium Association, 2011).

Cadmium salts of organic acids (generally cadmium laurate or cadmium stearate, used in combination with barium sulfate) were widely used in the past as heat and light stabilizers for flexible polyvinyl chloride and other plastics (Herron, 2001; UNEP; 2008). Small quantities of cadmium are used in various alloys to improve their thermal and electrical conductivity, to increase the mechanical properties of the base alloy (e.g. strength, drawability, extrudability, hardness, wear resistance, tensile, and fatigue strength), or to lower the melting point. The metals most commonly alloyed with cadmium include copper, zinc, lead, tin, silver and other precious metals. Other minor uses of cadmium include cadmium telluride and cadmium sulfide in solar cells, and other semiconducting cadmium compounds in a variety of electronic applications (Morrow, 2001; UNEP, 2008; International Cadmium Association, 2011).

Traditionally, the most common end-use applications for cadmium were pigments, stabilizers, and coatings. However, in recent years, the use of cadmium for these purposes has declined, mainly due to concerns over the toxicity of cadmium, and the introduction of regulations, particularly in the European Union, restricting its use (National Resources Canada, 2007).

1.4 Environmental occurrence

Historical information on the occurrence of cadmium and cadmium compounds can be found in the previous *IARC Monograph* (IARC, 1993a).

Cadmium occurs naturally in the earth's crust and in ocean water. It is emitted to the environment as a result of both natural and anthropogenic activities. Natural sources of cadmium include volcanic activity, weathering of cadmium-containing rocks, sea spray, and mobilization of cadmium previously deposited in soils, sediments, landfills, etc. Anthropogenic sources of cadmium include the mining and smelting of zinc-bearing ores, the combustion of fossil fuels, waste incineration, and releases from tailings piles or municipal landfills (UNEP, 2008; ATSDR, 2008).

1.4.1 Natural occurrence

In the earth's crust, cadmium appears mainly in association with ores containing zinc, lead, and copper (in the form of complex oxides, sulfides, and carbonates). Elemental cadmium is a soft, silver-white metal, which is recovered as a by-product of zinc mining and refining. The average terrestrial abundance of cadmium is 0.1–0.2 mg/kg, although higher concentrations are found in zinc, lead, and copper ore deposits. Naturally occurring cadmium levels in ocean water range, on average, from < 5 to 110 ng/L. (National Resources Canada, 2007; ATSDR, 2008; UNEP, 2008)

1.4.2 Air

Particulate cadmium (as elemental cadmium and cadmium oxide, sulfide or chloride) is emitted to the atmosphere from both natural and anthropogenic sources. Weathering and erosion of cadmium-bearing rocks is the most important natural source of cadmium. Other natural sources include volcanoes, sea spray, and

forest fires. The principal anthropogenic sources are non-ferrous metal production and fossil fuel combustion, followed by ferrous metal production, waste incineration, and cement production (WHO, 2000; ATSDR, 2008; UNEP, 2008)

Cadmium does not break down in the environment. Atmospheric cadmium compounds are transported (sometimes for long distances) and deposited (onto surface soils and water) with minimal transformation in the atmosphere (ATSDR, 2008). There is uncertainty about the relative magnitude of natural emissions versus anthropogenic emissions. Total global anthropogenic emissions in the mid-1990s were estimated at approximately 3000 tonnes. During 1990–2003, anthropogenic emissions of cadmium reportedly decreased by about half in Europe, and by about two-thirds in Canada (UNEP, 2008).

Mean total cadmium concentrations in air vary according to proximity to industrial source, and to population density. Measurement data from northern Europe for the period 1980–88 were reported as being around 0.1 ng/m^3 in remote areas, 0.1–0.5 ng/m^3 in rural areas, 1–10 ng/m^3 in urban areas, and 1–20 ng/m^3 in industrial areas, with levels of up to 100 ng/m^3 being observed near emission sources (WHO, 2000). Similar variations were observed in the USA (UNEP, 2008).

1.4.3 Water

Cadmium enters the aquatic environment from numerous diffuse (e.g. agricultural and urban run-off, atmospheric fall-out) and point sources, both natural and anthropogenic. Weathering and erosion of cadmium-containing rocks result in the release of cadmium not only to the atmosphere, but also to the soil and the aquatic system (directly and through the deposition of airborne particles) (ATSDR, 2008; UNEP, 2008). Cadmium is released to the aquatic environment from a range of anthropogenic sources, including non-ferrous metal mining and smelting (from mine drainage water, waste water, tailing pond overflow, rainwater run-off from mine areas), plating operations, phosphate fertilizers, sewage-treatment plants, landfills, and hazardous waste sites (IARC, 1993a; ATSDR, 2008).

Weathering and erosion are estimated to contribute 15000 tonnes of cadmium annually to the global aquatic environment, while atmospheric fall-out (of anthropogenic and natural emissions) is estimated to contribute between 900 and 3600 tonnes (UNEP, 2008).

1.4.4 Soil and sediments

Natural and anthropogenic sources (e.g. mine/smelter wastes, commercial fertilizers derived from phosphate ores or sewage sludge, municipal waste landfills) contribute to the levels of cadmium found in soil and sediments. Wet or dry deposition of atmospheric cadmium on plants and soil can lead to cadmium entering the food-chain through foliar absorption or root uptake. The rate of cadmium transfer depends on a variety of factors, including deposition rates, type of soil and plant, the pH of the soil, humus content, availability of organic matter, treatment of the soil with fertilizers, meteorology, and the presence of other elements, such as zinc (WHO, 2000; UNEP, 2008). Reported sediment concentrations of cadmium range from 0.03–1 mg/kg in marine sediments to as high as 5 mg/kg in river and lake sediments (Nordic Council of Ministers, 2003). Relatively high concentrations of cadmium (> 1 mg/kg) have been measured in the soil near smelters and other industrialized areas (WHO, 2000).

1.5 Human exposure

1.5.1 Exposure of the general population

The non-smoking general population is exposed to cadmium primarily via ingestion of food and, to a lesser extent, via inhalation of

ambient air, ingestion of drinking-water, contaminated soil or dust. For the US population, the geometric mean daily intake of cadmium in food is estimated to be 18.9 μg/day. In most countries, the average daily intake of cadmium in food is in the range of 0.1–0.4 μg/kg body weight (CDC, 2005; ATSDR, 2008; UNEP, 2008; EFSA, 2009)

Because tobacco leaves naturally accumulate large amounts of cadmium (Morrow, 2001), cigarettes are a significant source of cadmium exposure for the smoking general population. It has been estimated that tobacco smokers are exposed to 1.7 μg cadmium per cigarette, and about 10% is inhaled when smoked (Morrow, 2001; NTP, 2005). Data on blood and urine levels of smokers are found in Section 1.6.

1.5.2 Occupational exposure

The main route of cadmium exposure in the occupational setting is via the respiratory tract, although there may be incidental ingestion of dust from contaminated hands, and food (ATSDR, 2008). Occupations in which the highest potential exposures occur include cadmium production and refining, Ni–Cd battery manufacture, cadmium pigment manufacture and formulation, cadmium alloy production, mechanical plating, zinc smelting, brazing with a silver–cadmium–silver alloy solder, and polyvinylchloride compounding. Although levels vary widely among the different industries, occupational exposures generally have decreased since the 1970s. For more details on historical occupational exposures to cadmium, see the previous *IARC Monograph* (IARC, 1993a).

Estimates of the number of workers potentially exposed to cadmium and cadmium compounds have been developed by CAREX in Europe. Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX (CARcinogen EXposure) database estimates that 207350 workers were exposed to cadmium and cadmium compounds in the European Union, with over 50% of workers employed in the construction (*n* = 32113), manufacture of fabricated metal products (*n* = 23541), non-ferrous base metal industries (*n* = 22290), manufacture of plastic products not elsewhere classified (*n* = 16493), personal and household services (*n* = 15004), and manufacture of machinery except electrical (*n* = 13266).

CAREX Canada estimates that 35000 Canadians (80% males) are exposed to cadmium in their workplaces (CAREX Canada, 2011). The largest exposed group are workers in polyvinyl chloride plastic product manufacturing (*n* = 12000), who are exposed to cadmium-bearing stabilizers. Other industries in which exposure occurs include: foundries, commercial and industrial machinery manufacturing, motor vehicle parts manufacture, architectural and structural metal manufacturing, non-ferrous metal (except aluminium) production and processing, metalworking machinery manufacturing, iron and steel mills and ferro-alloy manufacturing, alumina and aluminium production and processing, and other electrical equipment and component manufacture.

Data from studies published since the previous *IARC Monograph* on exposure to cadmium and cadmium compounds in different occupational situations are summarized below.

(a) Battery manufacture

Zhang *et al.* (2002) investigated the renal damage of cadmium-exposed workers in an Ni–Cd battery factory in the People's Republic of China between April and May 1998. Based on area sampling measurements collected during 1986–92, the geometric mean concentration of cadmium oxide dust was 2.17 mg/m^3, with a range of 0.1–32.8 mg/m^3. The overall geometric mean urinary cadmium concentration for the 214 workers was 12.8 μg/g creatinine (range of geometric means, 4.0–21.4 μg/g creatinine), and the overall geometric mean blood cadmium

concentration was 9.5 μg/L (range of geometric means, 3.8–17.4 μg/L).

Cumulative exposure to cadmium hydroxide in Ni–Cd battery workers in the United Kingdom (*n* = 926 male workers) was investigated during 1947–2000. Mean cadmium concentrations in air from personal samples were highest in the 1969–73 period (range, 0.88–3.99 mg/m^3), and were lowest in the 1989–92 period (range, 0.024–0.12 mg/m^3). Mean cadmium concentrations in air from static area samples were highest in the 1954–63 period (range, 0.35–1.29 mg/m^3), and were lowest in the 1989–92 period (range, 0.002–0.03 mg/m^3) (Sorahan & Esmen, 2004).

(b) Cadmium recovery

Occupational exposure to cadmium compounds (oxide, sulfide, and sulfate) was investigated in male production workers (*n* = 571) from a cadmium recovery facility in the USA during 1940–82. Estimates of airborne cadmium exposures in the production departments ranged from 0.2 (in the tankhouse) to 1.5 mg/m^3 (in the mixing, calcine and retort departments) before 1950, and from 0.02 (in the tankhouse) to 0.6 mg/m^3 (in the sampling and roaster departments) for the 1965–76 time period (Sorahan & Lancashire, 1997).

(c) Cadmium alloy production

Occupational exposure to cadmium oxide fumes was investigated in 347 copper–cadmium alloy workers, 624 workers employed in the vicinity of copper–cadmium alloy work, and 521 iron and brass foundry workers in England and Wales during 1922–80. Based on a review of 933 measurements of airborne cadmium made during 1951–83 (697 area samples, 236 personal samples), cumulative cadmium exposures were estimated to be 600 μg/m^3 for the 1926–30 time period, dropping to an estimated 56 μg/m^3 by the 1980s (Sorahan *et al.*, 1995).

(d) Smelting

Occupational exposure to cadmium was investigated in 1462 male employees in a tin smelter in the United Kingdom during 1972–91. Annual average exposures in the principal process areas were reported. Average air levels were negligible in the dry-refining and electro-refining areas, low in the raw materials handling and roasters and ball mill areas (range of averages, 0.005–0.008 mg/m^3), and moderate in the sintering and blast furnace areas (range of averages, 0.04–0.08 mg/m^3) (Jones *et al.*, 2007).

(e) Vehicle manufacture

Wang *et al.* (2006) evaluated the exposure to metals of 82 welders and 51 operators in two vehicle-manufacturing plants in China. The geometric mean concentration of cadmium in the blood of welders was 3.54 μg/L (range, 0.2–12.5 μg/L), and was significantly higher than the control group concentration of 0.79 μg/L (range, 0.1–4.8 μg/L).

(f) Population-based surveys

Yassin & Martonik (2004) calculated the prevalence and mean urinary cadmium levels for all US workers, based on data collected from 11228 US workers aged 18–64 years who participated in the Third National Health and Nutrition Examination Survey (NHANES III, 1988–94). For all workers, urinary cadmium levels were in the range of 0.01–15.57 μg/L, with a geometric mean of 0.30 μg/L (0.28μg/g creatinine). The prevalence of elevated urinary cadmium levels was reported on the basis of the following ranges: ≥ 15 μg/L, ≥ 10 μg/L, ≥ 5 μg/L, and ≥ 3 μg/L. For all US workers aged 18–64 years, the prevalence of urinary cadmium levels ≥ 5 μg/L was 0.42% (*n* = 551000), for levels ≥ 10 μg/L, 0.06% (*n* = 78 471), and for levels ≥ 15 μg/L, 0.0028% (*n* = 3907). The proportion of workers with elevated urinary cadmium varied by occupation and industry. Within industry, urinary

cadmium levels ≥ 10 μg/L were twice as prevalent among workers in the metal industry compared to workers in the manufacturing industry (0.45% versus 0.26%). Within occupation, urinary cadmium levels ≥ 5 μg/L were 12 times as prevalent among vehicle mechanics than in transportation workers (1.71% versus 0.14%), and five times as prevalent in construction workers than in agriculture workers (0.73% versus 0.14%).

1.5.3 Dietary exposure

Low levels of cadmium have been measured in most foodstuffs (average concentrations are less than 0.02 μg/g). Factors influencing cadmium levels in food include: food type (e.g. seafood or leafy vegetables versus meat or dairy), growing conditions (e.g. soil type, water), agricultural and cultivation practices, meteorological conditions (i.e. rate of atmospheric deposition), and anthropogenic contamination of soil or aquatic system (UNEP, 2008; EFSA, 2009; WHO, 2011). Highly contaminated areas have higher cadmium concentrations in locally produced food, and the use of cadmium-containing fertilizers in agriculture increase cadmium concentrations in the crops, and derived products.

High concentrations of cadmium are found in leafy vegetables (e.g. lettuce, spinach), starchy roots (e.g. potatoes), cereals and grains, nuts and pulses (e.g. peanuts, soybeans, sunflower seeds). Lower concentrations of cadmium are found in meat and fish, with the exception of certain shellfish (e.g. oysters), and certain organ meats (e.g. kidney and liver), which concentrate cadmium. Weekly dietary intake estimates in the EU are in the range of 1.9–3.0 μg/kg body weight (mean, 2.3 μg/kg body weight) for non-vegetarians. Vegetarians, regular consumers of bivalve mollusks, and wild mushrooms are, respectively, estimated to have weekly dietary cadmium exposures of 5.4 μg, 4.6 μg, and 4.3 μg (per kg of body weight). On a body weight basis, estimated cadmium intakes are generally higher for infants and children than for adults (UNEP, 2008; EFSA, 2009).

1.5.4 Biomarkers of exposure

Several analytical procedures are available for measuring cadmium concentrations in biological samples. These include: atomic absorption spectroscopy (AAS), electrothermal atomic absorption spectroscopy (ET-AAS), flame atomic absorption, graphite furnace atomic absorption, inductively coupled plasma atomic emission spectroscopy (ICP-AES), inductively coupled plasma mass spectrometry (ICP-MS), neutron activation analysis, potentiometric stripping analysis, radiochemical neutron activation analysis, X-ray fluorescence, and treatment with methyl isobutyl ketone, ammonium pyrrolidenedithiocarbamate, or 13-bis[2-(pyridyl)ethylidene]thiocarbonhydride. The choice of analytical method is determined by several factors, including the sample matrix available (i.e. blood, plasma, serum, tissue, milk, hair, kidney, liver, muscle, urine, or teeth), and the detection limit required (ATSDR, 2008).

Cadmium in blood is used as an indicator of both recent and cumulative exposures, and urinary cadmium predominantly reflects cumulative exposure and the concentration of cadmium in the kidney (CDC, 2005). In the general population, normal blood cadmium concentrations are in the range of 0.4–1.0 μg/L for non-smokers and 1.4–4 μg/L for smokers, although much higher levels have been reported for environmental exposure (above 10 μg/L), and occupational exposure (up to 50 μg/L) (UNEP, 2008). Women typically have higher urinary cadmium concentrations than men, in part perhaps magnified by adjustment for creatinine excretion, which is lower in women (EFSA, 2009).

In a general population survey of approximately 4700 adults in Germany, Becker *et al.* (2002, 2003) found geometric mean cadmium levels of 0.44 μg/L in blood, and 0.23 μg/L in

urine. Smokers had a blood level of 1.1 μg/L, and non-smokers a level of 0.28 μg/L. Smokers had a urine level of 0.29 μg/L, former smokers 0.25 μg/L, and never-smokers 0.18 μg/L.

A study by the Centers for Disease Control and Prevention in the USA based on data from a random sample of people (National Health and Nutrition Examination Survey 1999–2002), found that the mean blood concentration of cadmium was 0.41 μg/L (n = 7970), and the 95th percentile blood concentration was 1.3 μg/L; the mean urine concentration of cadmium was 0.91 μg/L (n = 2257), and the 95th percentile blood concentration was 1.2 μg/L (CDC, 2005). NHANES data for workers in the period 1988–94 (urinary cadmium) are presented in Section 1.5.2 (Yassin & Martonik, 2004).

In an investigation of non-occupational cadmium exposure of 52 adult women in Bangkok, Thailand, Zhang *et al.* (1999) found a geometric mean level of cadmium in blood of 0.41 μg/L and 1.40 μg/g creatinine in urine. These were the lowest when compared to four neighbouring cities in South-eastern Asia (Kuala Lumpur, 0.74 μg/L and 1.51 μg/g; Manila, 0.47 μg/L and 1.21 μg/g; Nanning, 0.71 μg/L and 1.87 μg/g; and Tainan, 0.83 μg/L and 1.59 μg/g).

2. Cancer in Humans

The previous *IARC Monograph* on beryllium and beryllium compounds conclusion was based largely on evidence of increased lung cancer risk among workers exposed to cadmium (IARC, 1993b).

2.1 Cancer of the lung

In two small copper–cadmium alloy plants in the United Kingdom, the rate of mortality from lung cancer was increased in one but decreased in the other (Holden, 1980). The follow-up was extended by Sorahan *et al.* (1995) who documented increased risks of lung cancer in vicinity workers only, and an increased risk of non-malignant diseases of the respiratory system at higher cumulative cadmium exposures [Although an increased risk of lung cancer was not documented in this study, the Working Group noted that cases of lung cancer could potentially be misclassified as non-malignant disease. There was some population overlap between these studies.]

For cadmium-processing workers from 17 plants in the United Kingdom, mortality from lung cancer was significantly increased (standardized mortality ratio [SMR], 1.12; 95%CI: 1.00–1.24), with apparent positive trends with duration of employment and with intensity of exposure (Kazantzis & Blanks, 1992). The increase in lung cancer risk was stronger in the small proportion of workers with high cadmium exposure (SMR, 1.62; 95%CI: 0.89–2.73).

Follow-up of the United Kingdom Ni–Cd battery workers confirmed a slight increase in SMR for lung cancer associated with duration of employment in high-exposure jobs (Sorahan, 1987). Although not associated with cumulative exposure to cadmium, a significant increase in the SMR for cancers of the pharynx was also seen, and a non-significantly increased SMR for lung cancer was observed (Sorahan & Esmen, 2004).

An increase in mortality rates from lung cancer was detected in a small cohort of individuals who worked in the Ni–Cd battery-producing industry in Sweden, and who had the longest duration of employment and latency (Elinder *et al.*, 1985). Further follow-up showed an SMR for lung cancer in male battery workers of 1.76 (95%CI: 1.01–2.87), although without association with estimated total cadmium exposure (Järup *et al.*, 1998).

Excess mortality from lung cancer was reported among workers employed in a US cadmium recovery plant, which had been an arsenic smelter until 1925 (Lemen *et al.*, 1976),

and a dose–response relationship was demonstrated between the estimated cumulative exposure to cadmium and lung cancer risk (Stayner *et al.*, 1993). The dose–response relationship was unlikely to be due to confounding by cigarette smoking, and the relationship persisted among workers employed after 1940, when little arsenic was present in feedstock (Stayner *et al.*, 1993). The US Occupational Safety and Health Administration (OSHA) estimated that exposure to arsenic would have resulted in no more than one case of lung cancer death in this cohort. Using detailed job histories and dust measurements from the same US plant, Sorahan & Lancashire (1997) estimated total cadmium exposure, and identified workers with and without high potential for exposure to arsenic. Relative to the workers in the lowest cumulative exposure category, increased SMRs for lung cancer were found among the workers in higher exposure categories, especially after a lag time of 10 or 20 years. However, significant excess risks of lung cancer were found only for the early years of operation, when exposures to cadmium occurred in the presence of high arsenic exposures. For workers only employed in jobs with little or no exposure to arsenic, cumulative exposure to cadmium was weakly associated with lung cancer mortality. A subsequent analysis of the arsenic-exposed component of this cohort (Sorahan, 2009) showed a statistically significant reduction in risk of lung cancer SMRs in relation to time since leaving employment with arsenic exposure. This pattern was interpreted by the author as implying a late-stage action of arsenic, and a role for arsenic and not cadmium in the causation of lung cancer in this cohort. [The Working Group found this indirect argument against a role for cadmium not to be convincing. The Working Group noted that the population overlapped between these studies.]

In Belgium, Nawrot *et al.* (2006) studied subjects residing near three zinc smelters and also subjects from the area away from the cadmium pollution for the incidence of cancer from initial examinations in 1985–89 to 2004. Using urinary cadmium excretion and cadmium in garden soil as exposure indicators, the hazard ratio for lung cancer was 1.70 (95%CI: 1.13–2.57) for a doubling of the 24-hour urinary cadmium excretion, 4.17 (95%CI: 1.21–14.4) for residence in the high-exposure area versus the low-exposure area, and 1.57 (95%CI: 1.11–2.24) for a doubling of the cadmium concentration in soil. Overall cancer was also increased in the high-exposure group. Information on smoking was included in the adjustments. Data on urinary cadmium excretion adjusted for arsenic suggested that arsenic exposure alone could not explain the observed increases in risk.

See Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-03-Table2.1.pdf

2.2 Cancer of the prostate

Following a report of the occurrence of cancer of the prostate in a small group of workers employed in a plant manufacturing Ni–Cd batteries in the United Kingdom (Potts, 1965), a series of analyses of different occupational cohorts were undertaken, which did not confirm the excess (Kipling & Waterhouse, 1967; Kjellström *et al.*, 1979; Holden, 1980; Sorahan & Waterhouse, 1983; Elinder *et al.*, 1985; Thun *et al.*, 1985; Sorahan, 1987; Kazantzis & Blanks, 1992; Sorahan & Esmen, 2004). Some of these studies reported a non-significantly increased risk for cancer of the prostate among cadmium-exposed workers, but the results were inconsistent, and mostly based on small numbers of cases. Sahmoun *et al.* (2005) calculated a weighted SMR from four studies of Ni–Cd battery production workers who were highly exposed to cadmium. The summary SMR was 1.26 (95%CI: 0.83–1.84) based on 27 deaths. [The Working Group noted that these populations overlapped.] See Table 2.2

available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-03-Table2.2.pdf.

Slightly increased odds ratios for cancer of the prostate were also reported from a case–control study nested within occupational cohorts (Armstrong & Kazantzis, 1985). A hospital-based case–control study using cadmium measurements in toenails (Vinceti *et al.*, 2007) showed a significantly increased odds ratio at the highest concentrations. A case–control study nested within a cohort did not find this association, using the same biological sample collected at baseline as the exposure measure (Platz *et al.*, 2002). [The Working Group noted that the exposure in the second study was lower than in the first, and that the cadmium concentration in toenails may represent a prediagnostic retention level of unknown validity as a measure of long-term exposure.]

A descriptive study from cadmium-polluted areas in Japan reported an increased mortality from cancer of the prostate in two of four areas studied (Shigematsu *et al.*, 1982). Using increased urinary excretion of β_2-microglobulin as a marker of cadmium toxicity within the Nagasaki Prefecture, increased cancer mortality (relative risk [RR], 2.58; 95%CI: 1.25–5.36) and cancer incidence (RR, 1.79; 95%CI: 0.84–3.82) were found among the subjects with signs of cadmium toxicity (Arisawa *et al.*, 2001, 2007). Numbers for individual cancer sites were too low to allow for detailed analysis. [The Working Group noted that these populations overlapped.]

2.3 Other cancers

Other cancer sites, such as the pancreas, show a possible excess in SMRs, but only small numbers of cases have occurred in the occupational cohorts. In a small case–control study, the OR per ng/mL change in serum cadmium concentrations was estimated as 1.12 (95%CI: 1.04–1.23) for cancer of the pancreas (Kriegel *et al.*, 2006). [The Working Group noted that the serum concentration of cadmium is a less valid measure of cadmium exposure than concentrations in urine and whole blood.]

For cancer of the kidney, small numbers were reported in two of the cohort studies without any evidence of an association with cadmium exposure (Järup *et al.*, 1998; Sorahan & Esmen, 2004), but more recent data are available from case–control studies. A German multicentre study (Pesch *et al.*, 2000) included 935 cases of renal cell carcinoma and 4298 controls, and cadmium exposure was assessed by a national job–exposure matrix (JEM). In men and women, respectively, the OR was 1.4 (95%CI: 1.1–1.8) and 2.5 (95%CI: 1.2–5.3) for high exposure and 1.4 (95%CI: 0.9–2.1) and 2.2 (95%CI: 0.6–9.0) for very high exposure. In a Canadian study of 1279 cases of renal cell carcinoma and 5370 controls, self-reported cadmium exposure was a risk factor in males (OR, 1.7; 95%CI: 1.0–3.2) (Hu *et al.*, 2002). Most recently, a German hospital-based case–control study of 134 cases of renal cell carcinoma and 401 controls reported an OR for high exposure of 1.7 (95%CI: 0.7–4.2) (Brüning *et al.*, 2003).

A hypothesis-generating case–control study in the Montréal (Canada) metropolitan area showed that the bladder was the only one of 20 cancer sites to be associated with exposure to cadmium compounds (Siemiatycki, 1991). In a case–control study of transitional cell carcinoma of the bladder, the blood cadmium concentration was measured as an indicator of long-term cadmium exposure; the highest exposure tertile showed an OR of 5.7 (95%CI: 3.3–9.9); adjustments included smoking and occupational exposures to polyaromatic hydrocarbons and aromatic amines (Kellen *et al.*, 2007).

In another study, increased cadmium concentrations were found in breast tissue, but the mean cadmium concentration found in breast cancer patients was not significantly different from that of controls (Antila *et al.*, 1996). A larger case–control study of breast cancer used urinary cadmium excretion levels as a measure

of cumulated cadmium exposure; each increase by 1.0 µg/g creatinine was associated with an OR of 2.09 (95%CI: 1.2–3.8) (McElroy *et al.*, 2006).

On the basis of food frequency questionnaires in 1987–90 and 1997, Åkesson *et al.* (2008) calculated dietary cadmium intakes; the highest tertile of cadmium exposure had an OR of 1.39 [95%CI: 1.04–1.86] for endometrial cancer in postmenopausal women. The association was stronger in never-smokers, in women with normal body mass index, and in non-users of postmenopausal hormones.

2.4 Synthesis

The assessment of cancer risks in occupational cohorts exposed to cadmium is constrained by the small number of long-term, highly exposed workers, the lack of historical data on exposure to cadmium, particularly for the non-US plants, and the inability to define and examine a gradient of cumulative exposure across studies. Confounding by cigarette smoking in relation to the assessment of lung cancer risk among cadmium-exposed workers was addressed directly only in the study from the USA. Some other studies provided analyses based on internal comparisons, which are not likely to be affected by this problem of confounding. Few studies were able to control the confounding effect of co-exposure to other substances, particularly arsenic and nickel; however, the analyses of workers with low levels of exposure to arsenic still showed an increased lung cancer risk associated with cadmium exposure. Additional support for a cadmium-linked lung cancer risk comes from a prospective population-based study in environmentally polluted areas in Belgium.

The results of the studies on cadmium exposure and the risk of prostate cancer are suggestive of an association, but the results are inconsistent. In studies of occupational cohorts exposed to cadmium, studies of people residing in cadmium-contaminated areas and case–control studies of individuals with prostate cancer, some studies reported an increased risk for prostate cancer, while other studies did not indicate the same. The results from cohort studies are supported by a hospital-based case–control study that included highly exposed subjects.

Case–control studies suggest that other cancer sites, such as the kidney, and perhaps also the bladder, the breast, and the endometrium may show increased risks associated with dietary or respiratory cadmium exposure. [The Working Group noted that although case–control studies may be subject to bias from exposure misclassification, some studies considered have the strength of inclusion of blood or urine cadmium analyses that provide individual exposure data.]

3. Cancer in Experimental Animals

Cadmium compounds have been tested for carcinogenicity by subcutaneous administration to rats, mice, and hamsters, by intramuscular injection to rats, by oral exposure to rats and mice, by intraperitoneal exposure to mice, by inhalation exposure to rats, mice and hamsters, and by intratracheal administration to rats.

Particularly relevant studies reviewed in the previous *IARC Monograph* (IARC, 1993b) were reconsidered in this evaluation.

All cadmium compounds tested were not carcinogenic by all routes tested but most studies performed provided evidence for cadmium-induced carcinogenicity in animals.

3.1 Oral administration

Oral administration of cadmium chloride to rats increased the incidence of large granular lymphocytes, leukaemia, prostate tumours, and testis tumours in Wistar rats (Waalkes & Rehm, 1992). Noble rats exposed to oral cadmium chloride developed prostate hyperplasia (Waalkes *et al.*, 1999b).

See Table 3.1.

Table 3.1 Studies of cancer in experimental animals exposed to cadmium (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar WF/NCr (M) 77 wk Waalkes & Rehm (1992)	Cadmium chloride 0, 25, 50, 100 or 200 ppm in diet Also fed previous diets with zinc levels of 60 ppm (zinc adequate), 7 ppm (zinc deficient) for 2 wk 28/group 56 pooled controls	Prostate (tumours): 4/26 (15%) cadmium (50ppm) vs 1/54 (2%) pooled controls High-dose cadmium + zinc deficient: Testis (tumours)– 6/27 (22%) vs 1/28 (3%) controls Leukaemia (LGL): 7/25 (28%) vs pooled controls 3/55 (5%)	$P < 0.05$ $P < 0.05$	Age at start, 2 wk Prostate tumours not affected by zinc deficiency unless combined with prostate hyperplasias No increase in testis tumours with cadmium alone
Rat, Noble NBL/Cr (M) 102 wk Waalkes *et al.* (1999b)	Cadmium chloride 0, 25, 50, 100, 200 ppm in drinking-water 30/group	Prostate (dorsolateral and ventral; hyperplasias): 6 (21%), 12 (46%), 13 (50%), 6 (21%), 4 (15%) Testis (tumours): 2/29 (7%), 2/30 (7%), 3/30 (10%), 4/30 (13%), 5/28 (18%) Adrenal gland (pheochromocytomas): 2 (7%), 3 (10%), 8 (27%), 6 (20%), 3 (10%)	$P < 0.05$ vs control (Groups 2 & 3) NR $P < 0.05$ (mid-dose)	Age at start, 10 wk No dose response to induction of any tumour type

d, day or days; h, hour or hours; mo, month or months; LGL, large granular lymphocyte; NR, not reported; NS, not significant; vs, versus; wk, week or weeks

3.2 Inhalation and intratracheal administration

3.2.1 Rat

Inhalation exposure to cadmium chloride caused lung tumours in rats (Takenaka *et al.*, 1983; Glaser *et al.*, 1990). Cadmium sulfate, cadmium oxide, cadmium oxide fume and dust also caused lung tumours in rats (Glaser *et al.*, 1990).

Intratracheal administration of cadmium chloride and cadmium sulfide caused lung tumours in rats (Oberdörster & Cherian, 1992).

3.2.2 Hamster

Cadmium chloride, cadmium sulfate, cadmium sulfide, and cadmium oxide fume did not cause lung tumours in hamsters (Heinrich *et al.*, 1989; Heinrich, 1992).

See Table 3.2.

3.3 Subcutaneous administration

Many of the earliest carcinogenicity studies with cadmium compounds in rodents involved subcutaneous or intramuscular administration. In most studies, injection-site sarcomas developed in rats and mice. Mice were generally less susceptible than were rats. The earlier studies are reviewed in the previous *IARC Monograph*, and are not reviewed here, in part, because larger and better designed studies were published after 1993.

3.3.1 Mouse

Subcutaneous administration of cadmium chloride caused lymphomas, lung tumours (Waalkes & Rehm, 1994), and injection-site sarcomas (Waalkes *et al.*, 1991a; Waalkes & Rehm, 1994) in mice.

3.3.2 Rat

Subcutaneous administration of cadmium chloride caused injection-site sarcomas (Waalkes *et al.*, 1988, 1989, 1991b, 1997, 1999a, 2000; IARC, 1993b; Shirai *et al.*, 1993), and testis (interstitial cell) tumours in rats (Waalkes *et al.*, 1988, 1989, 1997, 1999b, 2000). Cadmium chloride caused prostate tumours and/or preneoplastic lesions in Wistar and Noble rats (Waalkes *et al.*, 1988, 1999b), but not in other studies in F344 or Wistar Furth rats (Waalkes *et al.*, 1991c, 2000; Shirai *et al.*, 1993).

3.3.3 Hamster

A single injection of cadmium chloride did not induce tumours in hamsters (Waalkes & Rehm, 1998).

A variety of cadmium compounds and metallic cadmium caused local sarcomas in rats or mice (IARC, 1993b).

See Table 3.3.

3.4 Administration with known carcinogens or other agents

The incidence of injection-site sarcomas in Wistar rats induced by cadmium chloride was significantly reduced by both the subcutaneous and oral administration of zinc (Waalkes *et al.*, 1989). Testicular tumours induced by subcutaneously administered cadmium chloride were inhibited by zinc, and were found to be associated with a reduction of the chronic degenerative testicular lesions induced by cadmium chloride (Waalkes *et al.*, 1989).

Testosterone implantation eliminated both cadmium-induced and spontaneous testis tumours in F344 rats but had no effect on cadmium-induced chronic testicular degeneration (Waalkes *et al.*, 1997).

Table 3.2 Studies of cancer in experimental animals exposed to cadmium (inhalation and intratracheal exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Inhalation				
Rat, Wistar, TNO/W75 (M) 31 mo Takenaka *et al.* (1983)	Cadmium chloride 12.5, 25 or 50 µg/m^3, 23 h/d, 7 d/wk for 18 mo 40/group	Lung (adenocarcinomas): 0/38, 6/39 (15%), 20/38 (52%), 25/35 (71%)	[$P < 0.0001$; Groups 3 & 4]	Age at start, 6 wk
Rat, Wistar, TNO/W75 > BOR-WISW (M, F) 31 mo Glaser *et al.* (1990)	0 to 900 µg/m^3 of cadmium chloride, cadmium sulfate, cadmium oxide, cadmium oxide fume, zinc oxide dust, and cadmium oxide dust, 40 h/wk for 18 mo Groups of 20–40 males, 20 females	All forms increased lung tumour incidence, 18/20 (90%) in cadmium sulfate females, 0/20 in controls from 31 experimental groups Controls, males 0/40, females 0/20 High doses > 75% incidences	[$P < 0.0001$]	Age at start, 9 wk Problem with concentration of cadmium in cadmium oxide fume Data from 31 experimental groups in Table 13, p.166, Volume 58 (IARC, 1993b)
Intratracheal				
Rat, Wistar (F) 124 wk Oberdörster & Cherian (1992)	Cadmium chloride or cadmium oxide 20 weekly 1 or 3 µg or 15 weekly 9 µg Cadmium sulfide 10 weekly 63, 250 or 1000 µg (purity 99%) Controls received 20x0.3ml saline	Lung (tumours): Cadmium chloride– Controls, 0/40; 20, 0/38; 60, 3/40 (7%); 135, 2/36 (6%) Cadmium oxide– 20, 2/37 (5%); 60, 2/40 (5%); 135, 0/39 Cadmium sulfide– 630, 2/39 (5%); 2500, 8/36 (22%); 10000, 7/36 (19%)	$P < 0.01$ trend test NS $P = 0.0005$ trend test	Cadmium chloride and cadmium sulfide purity, 99%

d, day or days; h, hour or hours; mo, month or months; NR, not reported; NS, not significant; wk, week or weeks

Table 3.3 Studies of cancer in experimental animals exposed to cadmium (subcutaneous or intramuscular exposure; for years < 1993, only selected references included)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar Crl WI BR (M) 104 wk Waalkes *et al.* (1988)	Cadmium chloride Single s.c. 0, 1, 2.5, 5, 10, 20, or 40 µmol/kg bw; 5 µmol/kg 4 × 5 and 10 µmol/kg 1 × each, 5 and 20 µmol/kg 1 × each (time 0 (low dose) and 48 h (high dose)) 30/group 45 pooled controls	Injection site (mostly sarcomas, also fibromas, epithelial tumours): 2/45 (4%), 1/30 (3%), 0/29, 1/30 (3%), 2/30 (7%), 1/29 (3%), *14/30 (47%) 0/30, 1/30 (3%), *8/30 (27%)	$P < 0.05$ from pooled control	Age at start, 6 wk High dose cadmium reduced testicular tumour responses Prostate tumour response is not strong or a dose response
		Testis (tumours): 8/45 (18%), 1/30 (3%), 3/29 (10%), 3/30 (10%), 4/30 (13%), *21/29 (72%), *24/29 (83%) 4/30 (13%), 2/30 (7%), 5/30 (17%)	$P < 0.05$	
		Prostate (ventral lobe; tumours): 5/44 (11%), 6/27 (22%), *8/26 (31%), 4/28 (14%), 4/23 (17%), 4/26 (15%), 3/29 (10%) 2/26 (8%), 5/28 (18%), 6/28 (21%)	$P < 0.05$ from pooled control	
		Preneoplastic foci: Positive trend with single dose (data in chart)	NR	
		Pancreas (acinar and islet cell): Negative trend with dose	NR	

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Wistar (M) 104 wk Waalkes *et al.* (1989)	Cadmium chloride Single injection s.c. 30 µmole/kg 3 × zinc acetate 0.1, 0.3, 1.0 mmol/kg i.m. 30 mmole/kg cadmium chloride + zinc chloride 1 mmol/kg + zinc acetate in water 30/group	Injection site (sarcomas): 12/30 (40%), pooled controls 0/84 1 × zinc reduced incidence Testis (tumours): Cd 1 × 25/30 (83%), controls 9/83 (11%) Zinc, dose-dependent decrease Prostate (adenoma): i.m. Cd 11/26 (42%), Cd+zinc 8/27 (30%), i.m. Cd+s.c. zinc 7/28 (25%), controls 8/83 (10%)	$P < 0.05$ $P < 0.05$ $P < 0.05$	
Rat, F344 (M) 104 wk Waalkes *et al.* (1997)	Cadmium chloride 20 µmole/kg s.c. once/wk for 5 wk Testosterone implants, 10 interim sacrifices 50/group	Testis (tumours): Controls 24/40 (60%) Testosterone only *0/40 Cd only *34/40 (98%) Testosterone+Cd *†0/37	 *$P \leq 0.05$ from control †$P \leq 0.05$ from cadmium alone	Age at start, 10 wk
Rat, Noble, NBL/Cr (M) 72 wk Waalkes *et al.* (1999a)	Cadmium chloride Single injection s.c. 0, 1, 2, 4, 8, 16, 32 µmole/kg 30/group	Testis: 1/30 (3%), 0/30, 0/30, 1/30 (3%), 7/30 (23%), 29/30 (96%), 28/30 (93%) Injection site (sarcomas): 0/30, 0/30, 0/30, 0/30, 0/30, 0/30, 7/30 (22%), 11/30 (37%) Prostate (proliferative lesions): 9/25 (36%), 16/26 (62%), 19/29 (65%), 19/24 (79%), 17/27 (63%), 18/30 (60%), 15/29 (52%)	$P < 0.053$ (higher doses) $P < 0.05$ $P < 0.05$, three middle doses	Prostate hyperplasia only

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, WF/NCr, F344/NCr (M) 104 wk Waalkes *et al.* (2000)	Cadmium chloride Single injection, s.c. 0, 10, 20, 30 µmole/kg bw weekly for 18 wk, 3 µmole/kg 1 wk then weekly 17 × 30 µmole/kg 30/group	Injection site (sarcomas): WF–0/20, 1/29 (3%), 21/29 (72%), 23/28 (82%), 23/29 (79%) F344–0/30, 11/30 (37%), 17/30 (68%), 8/12 (67%), 18/30 (60%)	$P < 0.05$ WF, four highest doses; F344 all doses	No prostate tumours were reported
		Testis: WF–11/29 (38%), 27/29 (93%), 19/29 (65%), 15/28 (54%), 15/29 (52%) F344–29/30 (97%), 28/30 (93%), 14/25 (56%), 8/12 (67%), 12/30 (43%)	$P < 0.05$ WF, two lower doses; F344 reduction in three highest doses	Pituitary adenomas reduced in higher doses of WF rats
Mouse, DBA/2NCr, NFS/NCr 104 wk (Waalkes & Rehm, 1994)	Cadmium chloride 40 µmol/kg s.c. 1once or once/wk for 16 wk 30–40/group	Lymphomas: DBA–1X Cd, 11/23 (48%); 16 × Cd, *16/28 (57%) Controls, 7/27 (26%)	$P = 0.024$ trend test	Age, 8 wk Strain differences seen No testis tumours
		Injection site (sarcomas): NFS–1X Cd, 3/27 (11%); 16 × Cd, 3/32 (9%) Controls, 0/23	$P = 0.016$ trend test	
		Lung: NFS–1X Cd, *21/28 (75%); 16 × Cd, 9/35 (26%) Controls, 6/25 (24%)		

h, hour or hours; i.m., intramuscular; NR, not reported; s.c., subcutaneous; wk, week or weeks

3.5 Synthesis

By inhalation, various cadmium compounds induce lung tumours in rats (cadmium chloride, cadmium oxide, cadmium oxide dust, cadmium oxide fumes, cadmium sulfide). Intratracheal administration of cadmium chloride and cadmium sulfide induces lung tumours in rats. In one study, subcutaneous injection of cadmium chloride caused lung tumours in mice. A variety of cadmium compounds and metallic cadmium cause local sarcomas in rats or mice. Administration of various salts of cadmium causes testicular tumours in rats. Cadmium chloride induced prostatic proliferative lesions and testicular tumours in rats after subcutaneous or oral administration.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

Inhalation is the major route of cadmium exposure in occupational settings, whereas most people in the general population are exposed to cadmium via the ingestion of both food and drinking-water. Exposure to cadmium particulates lead to cadmium absorption in animals and humans (IARC, 1993b).

In occupational settings, cadmium and cadmium compounds, being non-volatile, exist in air as fine particulates. Animal studies (Rusch *et al.*, 1986) have shown that lung retention may be up to 20%, especially after short-term exposure.

When ingested, most of the cadmium passes through the gastrointestinal tract without being absorbed. Estimates of the cadmium absorption rate in humans have been reported as 3–5% (Morgan & Sherlock, 1984) or 6.5% (Horiguchi *et al.*, 2004). Even lower rates have been reported for experimental animals, especially after long-term repeated exposures (Schäfer *et al.*, 1990).

When absorbed, cadmium will bind to metallothionein, forming a cadmium–metallothionein complex that is transferred (via blood) primarily to the liver and the kidney (Waalkes & Goering, 1990). Metallothionein is inducible in different tissues (e.g. liver, kidney, intestine, and lung) by exposure to various agents including cadmium (Waalkes & Goering, 1990). When transported to the kidney, cadmium–metallothionein is readily filtered at the glomerulus, and may be efficiently reabsorbed from the filtrate in the proximal tubules (Foulkes, 1978; Dorian *et al.*, 1992a). In the tubules, the protein portion is rapidly degraded to release cadmium (Dorian *et al.*, 1992b). Cadmium accumulates in kidney tubules, and causes damage to tubular cells, especially in the proximal tubules (Kasuya *et al.*, 1992).

Absorbed cadmium is excreted very slowly, and the amounts excreted into urine and faeces are approximately equal (Kjellström & Nordberg, 1978). In humans, half-life estimates are in the range of 7–16 years (Kjellström & Nordberg, 1978; Nordberg *et al.*, 2007).

4.2 Genetic and related effects

In rodent experiments, cadmium salts cause increased frequencies of micronuclei and chromosomal aberrations. In mammalian cells *in vitro*, cadmium compounds cause DNA strand breaks and chromosomal aberrations, and are weakly mutagenic, whereas in most bacterial assays, cadmium compounds are not mutagenic (Waalkes, 2003; DFG, 2006). Both soluble and insoluble cadmium compounds generally give comparable results in genotoxicity assays when tested in parallel.

Because cadmium salts do not cause DNA damage in cell extracts or with isolated DNA (Valverde *et al.*, 2001), the genotoxicity of cadmium has to be explained by indirect mechanisms. Frequently discussed mechanisms are related to oxidative stress, the inhibition of

DNA-repair systems, effects on cell proliferation, and on tumour-suppressor functions.

4.2.1 Induction of oxidative stress

Even though cadmium is not redox-active, it has been shown to induce oxidative stress, both *in vitro* and *in vivo*. Cadmium sulfide induced hydrogen peroxide formation in human polymorphonuclear leukocytes, and cadmium chloride enhanced the production of superoxide in rat and human phagocytes (Sugiyama, 1994). The induction of DNA strand breaks and chromosomal aberrations by cadmium in mammalian cells is suppressed by antioxidants and antioxidative enzymes (Ochi *et al.*, 1987; Stohs *et al.*, 2001; Valko *et al.*, 2006). Because cadmium does not undergo redox reactions under physiological conditions, the increased generation of reactive oxygen species levels and oxidative cellular damage may be due to the inhibitory effect of cadmium on antioxidant enzymes (Stohs *et al.*, 2001; Valko *et al.*, 2006) as well as on DNA-repair systems.

4.2.2 Inhibition of DNA repair

Cadmium is co-mutagenic and increases the mutagenicity of ultraviolet radiation, alkylation, and oxidation in mammalian cells. These effects are explained by the observation that cadmium inhibits several types of DNA-repair mechanisms, i.e. base excision, nucleotide excision, mismatch repair, and the elimination of the pre-mutagenic DNA precursor 7,8-dihydro-8-oxoguanine (Hartwig & Schwerdtle, 2002). In base-excision repair, low concentrations of cadmium that do not generate oxidative damage as such, very effectively inhibit the repair of oxidative DNA damage in mammalian cells (Dally & Hartwig, 1997; Fatur *et al.*, 2003). In nucleotide-excision repair, cadmium interferes with the removal of thymine dimers after UV irradiation by inhibiting the first step of this repair pathway, i.e. the incision at the DNA lesion (Hartwig & Schwerdtle, 2002; Fatur *et al.*, 2003). Furthermore, chronic exposure of yeast to very low cadmium concentrations results in hypermutability; and in human cell extracts, cadmium has been shown to inhibit DNA-mismatch repair (Jin *et al.*, 2003). Additionally, cadmium disturbs the removal of 8-oxo-dGTP from the nucleotide pool by inhibiting the 8-oxo-dGTPases of bacterial and human origin (Bialkowski & Kasprzak, 1998).

One molecular mechanism related to the inactivation of DNA-repair proteins involves the displacement by cadmium of zinc from zinc-finger structures in DNA-repair proteins such as xeroderma pigmentosum group A (XPA), which is required for nucleotide-excision repair, and formamidopyrimidine-DNA-glycosylase (Fpg), which is involved in base-excision repair in *E. coli* (Asmuss *et al.*, 2000). Cadmium also inhibits the function of human 8-oxoguanine-DNA-glycosylase (hOGG1), which is responsible for recognition and excision of the pre-mutagenic 7,8-dihydro-8-oxoguanine during base-excision repair in mammalian cells (Potts *et al.*, 2003). Even though hOGG1 contains no zinc-binding motif itself, the inhibition of its function is due to its downregulation as a result of diminished DNA-binding of the transcription factor SP1 that contains zinc-finger structures (Youn *et al.*, 2005). Finally, cadmium induces a conformational shift in the zinc-binding domain of the tumour-suppressor protein p53. Thus, in addition to inhibiting repair proteins directly, cadmium downregulates genes involved in DNA repair *in vivo* (Zhou *et al.*, 2004).

The impact of cadmium on DNA repair may be especially deleterious in cadmium-adapted cells. Cadmium induces several genes for cadmium and reactive oxygen species tolerance such as those coding for metallothionein, glutathione synthesis and function, catalase and superoxide dismutase (Stohs *et al.*, 2001). Hence, a condition for prolonged cell survival in the

presence of cadmium is established (Chubatsu *et al.*, 1992). Taking into account the impact of cadmium on DNA repair, tolerance to cadmium toxicity concurrently may constitute a greater opportunity for the induction of further critical mutations (Achanzar *et al.*, 2002).

4.2.3 Deregulation of cell proliferation and disturbance of tumour-suppressor functions

Cadmium interacts with a multitude of cellular signal transduction pathways, many of which associated with mitogenic signalling. Submicromolar concentrations of cadmium stimulated DNA synthesis, and the proliferation of rat myoblast cells (von Zglinicki *et al.*, 1992) and of rat macrophages (Misra *et al.*, 2002). In various cell types *in vitro*, cadmium induces the receptor-mediated release of the second messengers inositol-1,4,5-trisphosphate and calcium, activates various mitogenic protein kinases, transcription and translation factors, and induces the expression of cellular proto-oncogenes, *c-fos*, *c-myc*, and *c-jun* (Waisberg *et al.*, 2003). However, it should be noted that the activation of mitogen-activated protein kinases is not a sufficient condition for enhanced cell proliferation, because persistent low-dose exposure of cells to cadmium has been shown to result in sustained activation of protein kinase ERK, but also to caspase activation and apoptosis (Martin *et al.*, 2006). In addition to directly stimulating mitogenic signals, cadmium also inhibits the negative controls of cell proliferation. It inactivates the tumour-suppressor protein p53, and inhibits the p53 response to damaged DNA (Méplan *et al.*, 1999). This finding could be particularly important to explain the carcinogenicity of cadmium because p53 is required for cell-cycle control, DNA repair, and apoptosis; its inactivation would be expected to lead to genomic instability.

It was also reported that cadmium modulates steroid-hormone-dependent signalling in ovaries in rats, in a breast cancer cell line, and in cadmium-transformed prostate epithelial cells (Benbrahim-Tallaa *et al.*, 2007a; Brama *et al.*, 2007). Nevertheless, in in-vitro estrogenicity assays based on estrogen-receptor activity, no effect of cadmium was detected (Silva *et al.*, 2006). Whether or not cadmium promotes tumour growth by an estrogen-mediated mechanism is still unknown.

In addition to effects on genes and genetic stability, cadmium also exerts epigenetic effects, which may contribute to tumour development. During cadmium-induced cellular transformation, DNA–(cytosine-5) methyltransferase activity and global DNA methylation were reduced after 1 week of exposure to cadmium (Takiguchi *et al.*, 2003). Prolonged exposure to cadmium (~10 weeks) resulted in enhanced DNA–methyltransferase activity, and global DNA hypermethylation in these cells (Takiguchi *et al.*, 2003), and in human prostate epithelial cells (Benbrahim-Tallaa *et al.*, 2007b). Changes in DNA methylation is thought to have a tumour-promoting effect because a decrease in DNA methylation is associated with increased expression of cellular proto-oncogenes, and an increase of DNA methylation results in the silencing of tumour-suppressor genes.

4.3 Synthesis

Several mechanisms have been identified that potentially contribute to cadmium-induced carcinogenesis. Direct binding to DNA appears to be of minor importance, and mutagenic responses are weak. Convincing evidence exists on disturbances of DNA-repair and tumour-suppressor proteins, which lead to chromosomal damage and genomic instability. Further reported effects include changes in DNA-methylation patterns as well as interactions with signal-transduction processes, which may contribute to the deregulation of cell growth. However, it is not yet possible to assess the relative contributions of these latter mechanisms for cancer in humans.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of cadmium and cadmium compounds. Cadmium and cadmium compounds cause cancer of the lung. Also, positive associations have been observed between exposure to cadmium and cadmium compounds and cancer of the kidney and of the prostate.

There is *sufficient evidence* in experimental animals for the carcinogenicity of cadmium compounds.

There is *limited evidence* in experimental animals for the carcinogenicity of cadmium metal.

Cadmium and cadmium compounds are *carcinogenic to humans (Group 1).*

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CHROMIUM (VI) COMPOUNDS

Chromium (VI) compounds were considered by previous IARC Working Groups in 1972, 1979, 1982, 1987, and 1989 (IARC, 1973, 1979, 1980, 1982, 1987, 1990). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Synonyms, trade names, and molecular formulae for selected chromium (VI) compounds are presented in Table 1.1. This list is not exhaustive, nor does it necessarily reflect the commercial importance of the various chromium-containing substances. Rather, it is indicative of the range of chromium (VI) compounds available.

1.2 Chemical and physical properties of the agents

Chromium (VI), also known as hexavalent chromium, is the second most stable oxidation state of chromium. Rarely occurring naturally, most chromium (VI) compounds are manufactured (products or by-products). Chromium (VI) can be reduced to the more stable chromium (III) in the presence of reducing agents (e.g. iron) or oxidizable organic matter (OSHA, 2006). Selected chemical and physical properties of various chromium (VI) compounds are presented in the previous *IARC Monograph* (IARC, 1990).

Chromium (VI) compounds are customarily classed as soluble or insoluble in water. Examples of water-soluble chromium (VI) compounds are sodium chromate (873 g/L at 30 °C) and potassium chromate (629 g/L at 20 °C). Water-insoluble chromium (VI) compounds include barium chromate (2.6 mg/L at 20 °C), and lead chromate (0.17 mg/L at 20 °C) (Lide, 2008). Compounds with solubilities in the middle of this range are not easily classified, and technical-grade compounds, such as the various zinc chromates, can have a wide range of solubilities (IARC, 1990). In the United States of America, the Occupational Safety and Health Administration (OSHA) has divided chromium (VI) compounds and mixtures into the following three categories: water-insoluble (solubility < 0.01 g/L), slightly soluble (solubility 0.01 g/L–500 g/L), and, highly water-soluble (solubility ≥ 500 g/L) (OSHA, 2006).

Chromium (VI) compounds are mostly lemon-yellow to orange to dark red in colour. They are typically solid (i.e. crystalline, granular, or powdery) although one compound (chromyl chloride) is a dark red liquid that decomposes into chromate ion and hydrochloric acid in water (OSHA, 2006).

Table 1.1 Chemical names (CAS names are given in italics), synonyms, and molecular formulae of selected chromium (VI) compounds

Chemical name	CAS No.[a]	Synonyms	Formula[b]
Ammonium chromate	7788-98-9	Chromic acid, ammonium salt; *chromic acid (H_2CrO_4), diammonium salt*; diammonium chromate	$(NH_4)_2CrO_4$
Ammonium dichromate	7789-09-5	Ammonium bichromate; ammonium chromate; *chromic acid ($H_2Cr_2O_7$), diammonium salt*; diammonium dichromate; dichromic acid, diammonium salt	$(NH_4)_2Cr_2O_7$
Barium chromate	10294-40-3 (12000-34-9; 12 231-18-4)	Barium chromate (VI); barium chromate (1:1); barium chromate oxide; *chromic acid (H_2CrO_4), barium salt (1:1)*	$BaCrO_4$
Basic lead chromate	1344-38-3 (54692-53-4)	C.I. 77 601; *C.I. Pigment Orange 21*; C.I. Pigment Red; lead chromate oxide	$PbO.PbCrO_4$
Calcium chromate	13765-19-0	Calcium chromium oxide; calcium monochromate; *chromic acid (H_2CrO_4), calcium salt (1:1)*; C.I. 77223; C.I. Pigment Yellow 33	$CaCrO_4$
Chromium [VI] chloride	14986-48-2	Chromium hexachloride; *(OC-6–11)-chromium chloride ($CrCl_6$)*	$CrCl_6$
Chromium trioxide	1333-82-0 (12324-05-9; 12324-08-2)	Chromia; chromic acid; chromic (VI) acid; chromic acid, solid; chromic anhydride; chromic trioxide; *chromium oxide (CrO3)*; chromium (VI) oxide; chromium (6+) trioxide; monochromium trioxide	CrO_3
Chromyl chloride	14977-61-8	Chlorochromic anhydride; chromium chloride oxide; chromium dichloride dioxide; *chromium, dichlorodioxo-(T-4)*; chromium dioxide dichloride; chromium dioxychloride; chromium oxychloride; dichlorodioxochromium	CrO_2Cl_2
Lead chromate	7758-97-6 (8049-64-7) 1344-37-2	*Chromic acid (H_2CrO_4), lead (2+) salt (1:1)*; C.I. 77600; C.I. Pigment Yellow 34; Chrome Yellow; lead chromate/lead sulfate mixture	$PbCrO_4$
Molybdenum orange	12656-85-8	*C.I. Pigment Red 104*; lead chromate molybdate sulfate red	$PbMoO_4$ $PbCrO_4$ $PbSO_4$
Potassium chromate	7789-00-6	Bipotassium chromate; *chromic acid (H_2CrO_4), dipotassium salt*; dipotassium chromate; dipotassium monochromate; neutral potassium chromate; potassium chromate (VI)	K_2CrO_4
Potassium dichromate	7778-50-9	*Chromic acid ($H_2Cr_2O_7$), dipotassium salt*; dichromic acid, dipotassium salt; dipotassium bichromate; dipotassium dichromate; potassium bichromate; potassium dichromate (VI)	$K_2Cr_2O_7$
Sodium chromate	7775-11-3	*Chromic acid (H_2CrO_4), disodium salt*; chromium disodium oxide; chromium sodium oxide; disodium chromate; neutral sodium chromate; sodium chromium oxide	Na_2CrO_4

Table 1.1 (continued)

Chemical name	CAS No.[a]	Synonyms	Formula[b]
Sodium dichromate	10588-01-9 (12018-32-5)	Bichromate of soda; *chromic acid ($H_2Cr_2O_7$), disodium salt*; chromium sodium oxide; dichromic acid, disodium salt; disodium dichromate; sodium bichromate; sodium dichromate (VI)	$Na_2Cr_2O_7$
Strontium chromate	7789-06-2 (54322-60-0)	*Chromic acid (H_2CrO_4), strontium salt (1:1)*; C.I. Pigment Yellow 32; strontium chromate (VI); strontium chromate (1:1)	$SrCrO_4$
Zinc chromate[c]	13530-65-9 (1308-13-0; 1328-67-2; 14675-41-3)	*Chromic acid (H_2CrO_4), zinc salt (1:1)*; chromium zinc oxide; zinc chromium oxide; zinc tetraoxychromate; zinc tetroxychromate	$ZnCrO_4$
Zinc chromate hydroxides	15930-94-6 (12206-12-1; 66516-58-3)	Basic zinc chromate; chromic acid (H_6CrO_6), zinc salt (1:2); chromic acid (H_4CrO_5), zinc salt (1:2), monohydrate; chromium zinc hydroxide oxide; zinc chromate hydroxide; zinc chromate (VI) hydroxide; *zinc chromate oxide ($Zn_2(CrO_4)O$), monohydrate*; zinc hydroxychromate; zinc tetrahydroxychromate; zinc yellow[d]	$Zn_2CrO_4(OH)_2$ and others
Zinc potassium chromates (hydroxides)	11103-86-9 (12527-08-1; 37809-34-0)	Basic zinc potassium chromate; chromic acid ($H_6Cr_2O_9$), potassium zinc salt (1:1:2); *potassium hydroxyoctaoxodizincate dichromate (1-)*; potassium zinc chromate hydroxide; zinc yellow[d]	$KZn_2(CrO_4)_2(OH)$ and others

[a] Replaced CAS Registry numbers are given in parentheses.
[b] Compounds with the same synonym or trade name can have different formulae.
[c] The term ‘zinc chromate’ is also used to refer to a wide range of commercial zinc and zinc potassium chromates.
[d] ‘Zinc yellow’ can refer to several zinc chromate pigments; it has the CAS No. 37300-23-5.

1.3 Use of the agents

Chromium (VI) compounds are used widely in applications that include: pigment for textile dyes (e.g. ammonium dichromate, potassium chromate, sodium chromate), as well as for paints, inks, and plastics (e.g. lead chromate, zinc chromate, barium chromate, calcium chromate, potassium dichromate, sodium chromate); corrosion inhibitors (chromic trioxide, zinc chromate, barium chromate, calcium chromate, sodium chromate, strontium chromate); wood preservatives (chromium trioxide); metal finishing and chrome plating (chromium trioxide, strontium chromate), and leather tanning (ammonium dichromate). Chromium (VI) may be present as an impurity in Portland cement, and it can be generated and given off during casting, welding, and cutting operations (for example, of stainless steel), even if it was not originally present in its hexavalent state (NTP, 2005; OHCOW, 2005; OSHA, 2006).

1.4 Environmental occurrence

Chromium (VI) can occur naturally in the earth's crust, although it is primarily emitted to the environment as a result of anthropogenic activities. The occurrence and distribution of chromium in the environment has been extensively reviewed (Mukherjee, 1998; Kotaś & Stasicka, 2000; Rowbotham *et al.*, 2000; Ellis *et al.*, 2002; Paustenbach *et al.*, 2003; Guertin *et al.*, 2004; Reinds *et al.*, 2006; Krystek & Ritsema, 2007).

1.4.1 Natural occurrence

Only lead chromate (as crocoite) and potassium dichromate (as lopezite) are known to occur in nature (IARC, 1990).

1.4.2 Air

Chromium (VI) is reported to account for approximately one third of the 2700–2900 tons of chromium emitted to the atmosphere annually in the USA (ATSDR, 2008a). Based on US data collected from 2106 monitoring stations during 1977–84, the arithmetic mean concentrations of total chromium in the ambient air (urban, suburban, and rural) were in the range of 0.005–0.525 μg/m^3 (ATSDR, 2000).

1.4.3 Water

The concentration of chromium in uncontaminated waters is extremely low (< 1 μg/L or < 0.02 μmol/L). Anthropogenic activities (e.g. electroplating, leather tanning) and leaching of wastewater (e.g. from sites such as landfills) may cause contamination of the drinking-water (EVM, 2002). Chromium (VI) has been identified in surface water (n = 32) and groundwater samples (n = 113) collected from 120 hazardous waste sites in the USA (ATSDR, 2000), and 38% of municipal sources of drinking-water in California, USA, reportedly have levels of chromium (VI) greater than the detection limit of 1 μg/L (Sedman *et al.*, 2006).

1.4.4 Soil

Chromium is present in most soils in its trivalent form, although chromium (VI) can occur under oxidizing conditions (ATSDR, 2008a). In the USA, the geometric mean concentration of total chromium was 37.0 mg/kg (range, 1.0–2000 mg/kg) based on 1319 samples collected in coterminous soils (ATSDR, 2000).

1.4.5 Food

There is little information available on chromium (VI) in food. Most of the chromium ingested with food is chromium (III) (EVM, 2002).

1.4.6 Smoking

Tobacco smoke contains chromium (VI), and indoor air polluted by cigarette smoke can contain hundreds of times the amount of chromium (VI) found in outdoor air (Note for final read: this statement not referenced – remove or keep if reference found to support this).

1.5 Human exposure

1.5.1 Exposure of the general population

The general population residing in the vicinity of anthropogenic sources of chromium (VI) may be exposed through inhalation of ambient air or ingestion of contaminated drinking-water (ATSDR, 2000).

1.5.2 Occupational exposure

Inhalation of dusts, mists or fumes, and dermal contact with chromium-containing products are the main routes of occupational exposure. Industries and processes in which exposure to chromium (VI) occurs include: production, use and welding of chromium-containing metals and alloys (e.g. stainless steels, high-chromium steels); electroplating; production and use of chromium-containing compounds, such as pigments, paints (e.g. application in the aerospace industry and removal in construction and maritime industries), catalysts, chromic acid, tanning agents, and pesticides (OSHA, 2006).

Occupational exposures to several specific chromium compounds are reported in the previous *IARC Monograph* (IARC, 1990). With respect to chromium (VI) compounds, the most important exposures have been to sodium, potassium, calcium, and ammonium chromates and dichromates during chromate production; to chromium trioxide during chrome plating; to insoluble chromates of zinc and lead during pigment production and spray painting; to water-soluble alkaline chromates during steel smelting and welding; and, to other chromates during cement production and use (see Table 10; IARC, 1990, and OHCOW, 2005) for lists of occupations potentially exposed to chromium (VI)).

Estimates of the number of workers potentially exposed to chromium (VI) compounds have been developed by CAREX (CARcinogen EXposure) in Europe. Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX database estimates that 785692 workers were exposed to hexavalent chromium compounds in the European Union, with over 58% of workers employed in the following four industries: manufacture of fabricated metal products except machinery and equipment ($n = 178329$), manufacture of machinery except electrical ($n = 114452$), personal and household services ($n = 85616$), and manufacture of transport equipment ($n = 82359$). CAREX Canada (2011) estimates that 83000 Canadians are occupationally exposed to chromium (VI) compounds. Industries in which exposure occurred include: printing and support activities; architectural/structure metal manufacturing; agricultural, construction, mining machinery manufacturing; specialty trade contractors; boiler, tank, and container manufacturing; industrial machinery repair; auto repair; metalworking machinery manufacturing; steel product manufacturing; aluminum production; metal ore mining; coating, engraving, and heat treating. Welders were the largest occupational group exposed ($n = 19100$ men and 750 women).

Data on early occupational exposures to chromium (VI) are summarized in the previous *IARC Monograph* (IARC, 1990). Data from studies on chromium (VI) exposure published since the previous *IARC Monograph* are summarized below.

In a study to characterize occupational exposure to airborne particulate containing chromium, and to evaluate existing control technologies, the US National Institute for Occupational Safety and Health (NIOSH)

conducted 21 field surveys during 1999–2001 in selected industries. Industries and operations evaluated included: chromium electroplating facilities; welding in construction; metal cutting operations on chromium-containing materials in ship breaking; chromate-paint removal with abrasive blasting; atomized alloy-spray coating; foundry operations; printing; and the manufacture of refractory brick, coloured glass, prefabricated concrete products, and treated wood products. Personal breathing zone samples (full-shift and short-term) and general area samples were collected. Results were compared to the NIOSH recommended exposure limit (REL) of 1 μg/m³ (for a 10-hour exposure). Full-shift personal exposures to chromium (VI) were in the range of 3.0–16 μg/m³ at the electroplating facilities, and 2.4–55 μg/m³ at a painting and coating facility that used products containing chromium (VI) (Blade *et al.*, 2007).

NIOSH conducted a health hazard evaluation of worker exposures during the welding and manufacturing of stainless steel products and fabricated piping systems. Personal breathing zone air sampling concentrations of chromium (VI) were above the NIOSH REL. The highest concentrations for nickel and chromium (VI) occurred during welding operations inside large stainless steel pipes (0.26 mg/m³ and 0.36 mg/m³), and while welding fins on a large stainless steel pipe (Hall *et al.*, 2005).

As part of an international epidemiological study of workers in the pulp and paper industry, Teschke *et al.* (1999) assembled and analysed 7293 previously unpublished exposure measurements collected in non-production departments from 147 mills in 11 countries. Chromium (VI) compounds were reported in 26 time-weighted average (TWA) samples from nine mills, with a mean airborne chromium (VI) concentration of 63 μg/m³ (range, 0.04–1220 μg/m³).

Proctor *et al.* (2003) analysed more than 800 measurements of airborne chromium (VI) from 23 surveys conducted during 1943–71 at a chromate production plant in Painesville, Ohio, USA. The highest chromium (VI) concentrations recorded at the plant occurred in shipping (e.g. bagging of dichromate), lime and ash, and filtering operations (maximum yearly TWA concentrations of 8.9, 2.7, and 2.3 mg/m³, respectively). The data showed that concentrations in the indoor operating areas of the plant generally decreased over time, dropping from 0.72 mg/m³ in the 1940s, to 0.27 mg/m³ in 1957–64, and to 0.039 mg/m³ in 1965–72.

In a study to assess industry compliance with existing and proposed standards, Lurie & Wolfe (2002) conducted a secondary data analysis of 813 chromium (VI) measurements collected in 1990–2000 by OSHA. Chromium (VI) was not detected in 436 measurements. In the remaining samples, the median 8-hour TWA concentration was 10 mg/m³ (n = 197; range, 0.01–13960 mg/m³), and the median ceiling concentration was 40.5 mg/m³ (n = 180; range, 0.25–25000 mg/m³). In the plating and polishing industry, the median 8-hour TWA concentration was 8.2 mg/m³ (n = 65; range, 0.01–400 mg/m³), and the median ceiling concentration was 23 mg/m³ (n = 51; range, 1–410 mg/m³).

Luippold *et al.* (2005) examined the mortality of two cohorts of chromate production workers constituting the current US chromium chemical industry, after engineering controls were implemented. Personal air monitoring sampling for chromium (VI) at the two plants resulted in approximately 5230 personal air-monitoring measurements taken during 1974–88 for Plant 1, and 1200 measurements taken during 1981–98 for Plant 2. Personal levels of chromium (VI) exposure were very low at both plants (geometric mean, < 1.5 μg/m³ for most years; range of annual means, 0.36–4.36 μg/m³). At both plants, the work areas with the highest average exposures were generally less than 10 μg/m³ for most years.

In an occupational exposure study of chromium in an aircraft construction factory, personal airborne samples were collected in

a group of 16 workers over a 4-hour period, and urinary samples were collected from 55 workers at the beginning of their work shift (on Monday), and at the beginning and end of their work shift (on Friday). The geometric mean air concentration was 0.17 μg/m^3 (GSD, 5.35 μg/m^3; range, 0.02–1.5 μg/m^3). Geometric mean creatinine levels were as follows: pre-shift Monday, 0.63 μg/g (GSD, 0.53 μg/g; range, 0.23–2.9 μg/g); pre-shift Friday, 0.95 μg/g (GSD, 0.94 μg/g; range, 0.25–4.8 μg/g); and post-shift Friday, 0.91 μg/g (GSD, 1.38 μg/g; range, 0.16–7.7 μg/g) (Gianello *et al.*, 1998).

2. Cancer in Humans

2.1 Introduction

A large number of case reports dating to the late 19th and early-to-mid-20th centuries raised suspicions that workers in various industries with exposure to chromium compounds, including chromate production, production of chromate pigments and chromium plating may be at risk of developing various cancers (Newman, 1890; Pfeil, 1935; Teleky, 1936; IARC, 1990). Beginning in the mid-20th century, cohort studies were undertaken in these industries as well as in some other occupations and industries with potential exposure to chromium compounds, such as ferrochromium or stainless steel production, welding, leather tanning, and some others. By the 1980s considerable evidence had accumulated on cancer risks of chromium-exposed workers, and leading to the identification of chromium (VI) compounds as a human carcinogen (IARC, 1990).

The strongest evidence presented at the time concerned the lung. There was weaker and less consistent evidence of effects on gastrointestinal sites, mainly stomach, and some reports of excess risks at several other organs, such as pancreas, prostate and bladder. Furthermore, there were some case reports and small clusters of nasal or sinonasal cavity cancers in workers exposed to chromium (VI). Based on the review of the previous *IARC Monograph*, and on a subsequent review of relevant epidemiological evidence accumulated since then, the Working Group focused the current review on those sites for which the evidence indicates possible associations with chromium (VI) compounds, namely: lung, nose, and nasal sinus. Because of recent controversy regarding possible effects on stomach cancer (Proctor *et al.*, 2002; Beaumont *et al.*, 2008), the Working Group also reviewed relevant evidence for this organ. For other organs, the number of reports of excess risks is unremarkable in the context of the numbers of studies that have been conducted, and thus they have not been reviewed.

There have been at least 50 epidemiological studies that could be informative about cancer risks related to chromium (VI). Many of the studies have given rise to multiple reports; sometimes these simply represent follow-up updates, but often the different reports also present different types of analyses of subgroups or of case–control analyses within a cohort. Only a minority of the studies contain documented measurements of chromium (VI) exposure, particularly measurements that pertain to the era of exposure of the workforce that was investigated. It was therefore necessary to select and present the evidence according to the availability of relevant exposure information. The studies were triaged into the following categories:

1. Cohort studies in industries in which workers were highly likely to have been exposed at relatively high levels. This included workers in chromate production, chromate pigment production, and chromium electroplating.
2. Cohort studies in which workers were possibly exposed to relatively high levels but not with the same degree of certainty or concentration as those in category a. This included stainless steel welders.

3. Other studies in which workers may have been exposed to chromium (VI), but with lower likelihood or lower frequency or lower concentrations than workers in categories 1) and 2). Among the occupations/industries in this category were ferrochromium and stainless steel production, mild steel welding, general paint production, general spray painting, tanneries, gold mining, and nickel plating.

Studies in category 3) were not routinely included in the current review because there were sufficiently informative studies in categories 1) and 2), except if the authors presented information indicative of exposure to non-negligible levels of chromium (VI).

Most of the informative evidence comes from industry-based cohort studies, some of which have been complemented by nested case–control analyses. One of the main limitations of industry-based cohort studies is the usual absence of information on smoking and other potential confounders aside from age, sex, and race. Nonetheless, except for some case–control studies of nasal cancer, the Working Group relied on cohort studies to provide informative results.

For each study selected, the Working Group chose the most recent publication; occasionally there were results in earlier papers that were also deemed important to present here. Further, in each publication there are typically a large number of results presented by organ site, by demographic characteristics of workers, by some index of duration or dose of exposure, and sometimes by analysing the data in a nested case–control fashion. For the purposes of the current review, the Working Group selected the key results from each publication, typically including the most general result available for workers exposed to chromium (VI) as well as a result for a subgroup characterized by relatively high duration or dose of exposure, when there were enough numbers in such a category.

2.2 Cancer of the lung

Almost all of the relative risk estimates for cancer of the lung presented in Table 2.1 (available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-04-Table2.1.pdf) are greater than 1.0. Among chromate production workers, virtually all studies showed excess risks of lung cancer, except for a few estimates of risks for US workers hired since exposures were lowered (Luippold *et al.*, 2005), but these latter analyses had few subjects and low power.

Similarly, studies of chromate pigment production workers tended to show elevated risks of lung cancer in nearly all the cohorts and subcohorts reported, though not every relative risk estimate was statistically significant. Also, among chromium electroplating workers, there was a clear pattern of excess risks in most cohorts. Workers in other industries who may have had somewhat lower levels of chromium (VI) exposure than those in the previously mentioned industries, had a less convincing set of relative risk estimates, though nearly all were above 1.0.

A few of the cohort studies collected high-quality smoking histories, and incorporated these into nested case–control analyses; these tended to show elevated risks independent of smoking. Several other studies had collected partial or representative smoking frequencies among their workers, and for most of these studies, the main results were unlikely to have been meaningfully confounded by smoking patterns in the workers.

A recent meta-analysis estimated an overall standardized mortality ratio (SMR) of 1.41 (95%CI: 1.35–1.47) for lung cancer among 47 studies of workers with possible chromium (VI) exposure (Cole & Rodu, 2005). [The Working Group noted that because of the great difficulty in establishing equivalencies between different studies in terms of the types and levels of exposures to chromium (VI), the summary estimates are difficult to interpret. Further, it appears

that some of the study populations in that meta-analysis overlapped with each other.]

In aggregate, the results continue to show that exposure to chromium (VI) increases the risks of lung cancer.

Very few of the epidemiological studies provided results relating to specific chromium (VI) compounds. Workers in chromate production were likely to have been exposed to mixtures of sodium, potassium, calcium and ammonium chromates and dichromates; the highest and most consistent excess risks were observed in these cohorts. Workers in chromate pigment production and spray painting were likely to have been exposed to zinc and/or lead chromates, also resulting in high risks. Steel smelting and welding probably resulted in exposure to alkaline chromates, and risks reported in these cohorts tended to be less clear than among the chromate producers and the chromate pigment producers. Because there seemed to be increased risks in diverse industries involving exposure to a variety of chromium (VI) compounds of varying solubilities, this observation argues for a general carcinogenic effect of chromium (VI).

2.3 Cancer of the nose and nasal sinus

Cancer of the nose and nasal sinus is extremely rare, the incidence of which is roughly 1/100th of the incidence of cancer of the lung (Parkin *et al.*,1997). In fact, most cohorts of workers exposed to chromium (VI) do not report on of the incidence of nose and nasal sinus cancers. [The Working Group noted that this could mean there were none in the cohort or that the investigators did not examine and report it.]

Table 2.2 (available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-04-Table2.2.pdf) shows the nine (ten studies including Sorahan *et al.*, 1987) cohort studies that did report how many nasal cancers occurred. Combining those nine (ten) cohorts, there were mentions of 22 (25) cases of nasal or nasal sinus cancer. For the four cohorts that reported an expected as well as an observed number of cases, the aggregate was 12 observed and 1.5 expected giving an SMR of 8.0. Because several cohort studies failed to report any cases, it is difficult to integrate the appropriate observed and expected numbers from these studies into the overall estimate of risk from cohort studies. [The Working Group believed that many of the studies which made no report on nasal cancer actually had none.]

Case reports since the 1960s have reported 11 (12 including one case reported in Enterline, 1974) cases of nasal or nasal sinus cancer among chromate workers. Without any indication of person-years at risk, it is difficult to infer whether this represents an excess.

There have been three informative case–control studies on nasal and nasal sinus cancer. Two showed some indications of excess risk among workers with possible exposure to chromium (VI) compounds, but the study with the best exposure assessment protocol (Luce *et al.*, 1993) reported no excess risks for workers exposed to chromium (VI).

In aggregate, the epidemiological evidence remains suggestive but inconclusive regarding the effect of chromium (VI) on nasal and nasal sinus cancers. [The Working Group noted that systematic confounding by nickel exposure is unlikely in the cohorts presented in Table 2.2 online.]

2.4 Cancer of the stomach

There is little evidence of an association between exposure to chromium (VI) and cancer of the stomach; there are as many point estimates above 1.0 as there are below. There has been concern about possible hazards related to the ingestion of chromium (VI) in drinking-water, and one study in the People's Republic of China

(Zhang & Li, 1987) and a subsequent reanalysis of the Chinese data (Beaumont *et al.*, 2008) seem to indicate a somewhat elevated risk of stomach cancer in which drinking-water was heavily polluted by a ferrochromium plant. However, one single ecological study does not constitute rigorous evidence of an association between exposure to chromium (VI) and cancer of the stomach.

See Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-04-Table2.3.pdf.

2.5 Synthesis

The large majority of informative cohort studies indicate that there is an excess risk of lung cancer among workers exposed to chromium (VI), particularly in chromate production, chromate pigment production, and chromium electroplating. It is unlikely that any biases or chance can explain these findings.

There are some case reports, cohort studies and case–control studies that suggest a possible excess of cancer of the nose and nasal sinus among workers exposed to chromium (VI). However, this evidence is susceptible to publication and reporting biases because many of the cohort studies did not report on nasal cancers, and it is not clear how to evaluate the significance of the case reports.

There is little evidence that exposure to chromium (VI) causes stomach or other cancers.

3. Cancer in Experimental Animals

Chromium (VI) compounds have been tested for carcinogenicity by several routes in several animal species and strains (IARC, 1990), and the following paragraphs summarize some key findings from previous IARC evaluations of chromium (VI) compounds.

Calcium chromate induced lung tumours in mice (males and females combined) when given by inhalation (Nettesheim *et al.*, 1971) and local tumours when given by intramuscular administration (Payne, 1960). In rats it caused lung tumours (adenoma, squamous cell carcinoma, or adenocarcinoma) when given by intratracheal administration (Steinhoff *et al.*, 1986) or intrabronchial administration (Levy & Venitt, 1986), bronchial (carcinomas or squamous cell carcinomas) when administered by intrabronchial administration (Levy *et al.*, 1986), and local tumours in rats treated by intrapleural (Hueper, 1961; Hueper & Payne, 1962) or intramuscular administration (Hueper & Payne, 1959, 1962; Hueper, 1961; Roe & Carter, 1969).

Lead chromate (and its derived pigments), administered by subcutaneous injection (Maltoni, 1974, 1976; Maltoni *et al.*, 1982) or intramuscular injection cause malignant tumours at the site of injection and renal tumours (Furst *et al.*, 1976) in rats. Subcutaneous administration of basic lead chromate caused local sarcomas in rats (Maltoni, 1974, 1976; Maltoni *et al.*, 1982). In rats, zinc chromates caused bronchial carcinomas when administered by intrabronchial implantation (Levy *et al.*, 1986), and local tumours when given intrapleurally (Hueper, 1961), subcutaneously (Maltoni *et al.*, 1982) or intramuscularly (Hueper, 1961). Strontium chromate also caused bronchial carcinomas (intrabronchial implantation administration) (Levy *et al.*, 1986), and local sarcomas (intrapleural and intramuscular administration) in rats (Hueper, 1961).

Chromium trioxide when tested as a mist by inhalation caused nasal papillomas in mice (Adachi & Takemoto, 1987). Local tumours were observed in rats exposed to sintered chromium trioxide (Hueper & Payne, 1959). A low incidence of lung adenocarcinomas was induced after inhalation of chromium trioxide, and some lung tumours were observed in rats exposed by intrabronchial administration but neither were

statistically significant (Adachi *et al.*, 1986; Levy *et al.*, 1986; Levy & Venitt, 1986).

Sodium dichromate (when given by inhalation or intratracheal administration) caused lung tumours (benign and malignant) (Glaser *et al.*, 1986; Steinhoff *et al.*, 1986) in rats.

3.1 Studies published since the previous *IARC Monograph*

Since the previous *IARC Monograph* (IARC, 1990), studies in experimental animals have been conducted to evaluate oral exposure to chromium (VI). Table 3.1 summarizes the results of these studies, and the text below summarizes the major findings for each specific compound.

3.1.1 Sodium dichromate dihydrate

The National Toxicology Program (NTP) conducted 2-year drinking-water studies of sodium dichromate dihydrate in male and female B6C3F$_1$ mice, and in male and female F344 rats. In rats, sodium dichromate dihydrate significantly increased the incidence of squamous cell epithelium tumours of the oral mucosa or tongue in the high-dose groups (516 mg/L) of males and females. Trend analysis indicated a dose–response relationship in both males and females. In mice, sodium dichromate dihydrate significantly increased tumours (adenomas or carcinomas) of the small intestine (duodenum, jejunum, or ileum) in the two-highest dose groups of males (85.7 and 257.4 mg/L) and females (172 and 516 mg/L). Dose–response relationships were observed in both sexes (NTP, 2008).

3.1.2 Potassium chromate

Davidson *et al.* (2004) studied the effects of potassium chromate on ultraviolet(UV)-induced skin tumours in female hairless mice (CRL: SK1-hrBR). Mice were exposed to UV alone, various concentration of potassium chromate alone (given in the drinking-water), and UV together with various concentrations of potassium chromate. Administration of drinking-water containing potassium chromate did not induce skin tumours alone. However, chromate treatment significantly increased the multiplicity of UV-induced skin tumours, and the multiplicity of malignant UV-induced skin tumours. Similar results were found in male and female hairless mice (Uddin *et al.*, 2007). The analysis of skin indicated that UV treatment increased the level of chromium in the exposed skin (Davidson *et al.*, 2004).

3.2 Synthesis

The administration of calcium chromate in mice and sodium dichromate in rats by inhalation caused lung cancer. Calcium chromate and sodium dichromate administered by intratracheal instillation caused lung cancer in rats. Intratracheal administration of calcium chromate, zinc chromate, and strontium chromate caused lung cancer in rats. Several chromium compounds by repository injection (calcium chromate, lead chromate, zinc chromate, strontium chromate) caused local sarcomas. Oral administration of sodium dichromate to rats and mice caused cancer of the oral cavity and of the gastrointestinal tract. Potassium chromate given orally, although not given alone, enhanced UV-induced skin carcinogenesis, indicating tumour systemic effects.

Table 3.1 Studies of cancer in experimental animals exposed to chromium (VI) (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance[a]	Comments
Sodium dichromate dihydrate				
Rat, F344/N (M, F) 2 yr NTP (2008)	Drinking-water 0, 14.3, 57.3 172, 516 mg/L Average daily doses: M-0, 0.6, 2.2 6, 17 mg/kg bw F-0, 0.7, 2.7, 7, 20 mg/kg bw *ad libitum* 50/group/sex	Oral mucosa (squamous cell carcinomas):[b] M–0/50, 0/50, 0/49, 0/50, 6/49 (12%) F–0/50, 0/50, 0/50, 2/50 (4%), 11/50 (22%) Tongue (squamous cell papillomas or carcinomas): M–0, 1, 0, 0, 1 F–1, 1, 0, 1, 0 Oral mucosa or tongue:[c] M–0/50, 1/50 (2%), 0/49, 0/50, 7/49 (14%) F–1/50 (2%), 1/50 (2%), 0/50, 2/50 (4%), 11/50 (22%)	M: $P < 0.05$ (high dose); $P_{trend} < 0.001$ F: $P < 0.001$ (high dose); $P_{trend} < 0.001$ M: $P < 0.01$; $P_{trend} < 0.001$ F: $P < 0.01$ (high dose); $P_{trend} < 0.001$	Age at start, 6–7 wk 99.7% pure No treatment effects on survival Decreased bw in high-dose males and females Decreased water consumption of the 2 highest doses
Mouse, $B6C3F_1$ (M, F) 2 yr NTP(2008)	Drinking-water M: 0, 14.3, 28.6, 85.7, 257.4 mg/L F: 0, 14.3, 57.3, 172, 516 mg/L Average daily doses: M–0, 1.1, 2.6, 7, 17 mg/kg bw F–0, 1.1, 39.9, 9, 25 mg/kg bw *ad libitum* 50/group/sex	Small intestine (adenomas): M–1/50 (2%), 1/50 (2%), 1/50 (2%), 5/50 (10%), 17/50 (34%) F–0/50, 1/50 (2%), 2/50 (4%), 15/50 (30%), 16/50 (32%) Small intestine (carcinomas): M–0/50, 2/50 (4%), 1/50 (2%), 3/50 (6%), 5/50 (10%) F–1/50 (2%), 0/50, 2/50 (4%), 3/50 (6%), 7/50 (14%) Small intestine (adenomas or carcinomas):[d] M–1/50 (2%), 3/50 (6%), 2/50 (4%), 7/50 (14%), 20/50 (40%) F–1/50 (2%), 1/50 (2%), 4/50 (8%), 17/50 (34%), 22/50 (44%)	M: $P < 0.001$ (high dose); $P_{trend} < 0.001$ F: $P < 0.001$ (2 highest doses); $P_{trend} < 0.001$ M: $P < 0.05$ (high dose); $P_{trend} < 0.05$ F: $P < 0.05$ (high dose); $P_{trend} < 0.001$ M: $P < 0.001$ (high dose), $P < 0.05$ (85.7 mg/L), $P_{trend} < 0.001$ F: $P < 0.001$ (2 highest doses 172 and 516 mg); $P_{trend} < 0.001$	Age at start, 6–7 wk 99.7% pure No treatment effects on survival Decreased body weight in 2 highest female dose groups Decreased water consumption of the 2 highest doses (males and females) Most of the tumours were located in the duodenum

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance[a]	Comments
Potassium chromate (K_2CrO_4)				
Mouse, CRL: Sk1-hrBR (F) 224 d Davidson *et al.* (2004)	Group 1: Controls Group 2: UV only Group 3: 2.5 ppm K_2CrO_4 Group 4: 5 ppm K_2CrO_4 Group 5: UV +0.5 ppm K_2CrO_4 Group 6: UV + 2.5 ppm K_2CrO_4 Group 7: UV + 5 ppm K_2CrO_4: UV: 1 mo after K_2CrO_4 1.1 kJ/m^2 3 d/wk for 3 mo, followed by 1 wk break, and 1.3 kJ/m^2, 2 d/wk for 3 mo K_2CrO_4: 182 d, added to drinking-water every 7–10 d 120 animals	Skin (tumours): Groups 1, 3, 4–no tumours *Number of tumours (> 2mm/no of mice at 182 d):* Group 2–12/15 (0.8) Group 5–16/12 (1.39) Group 6–50/19 (2.63) Group 7–94/19 (5.02)	Group 6 vs Group 2, $P < 0.05$ Group 7 vs Group 2, $P < 0.01$	Age at start, 6 wk Chromium-only treatment had no effects on bw or toxicity Levels of chromium were measured in dorsal thoracic skin and abdominal skin in Groups 1, 4, and 7 UV + chromium had significantly higher chromium levels in back and underbelly skin

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance[a]	Comments
Mouse, CRL: Sk1-hrBR (M, F) 224 d Uddin *et al.* (2007)	Groups: treatment, *n* Group 1a: UV, 10 Group 1a: UV + 2.5 ppm K_2CrO_4, 10 Group 1c: UV + 5 ppm K_2CrO_4, 10 Group 2a: UV + 5 ppm K_2CrO_4, 10 Group 2b: UV + 5 ppm K_2CrO_4 + Vitamin E, 10 Group 2c: UV + 5 ppm K_2CrO_4 + selenium, 10 Mice administered K_2CrO_4 in drinking-water at 3 wk of age. 3 wk later UV treatment (1.0 kJ/m^2) 3 d/wk for 26 wk Vitamin E: 62.5 IU/kg Selenium: 5 mg/kg Group 1–males, Group 2–females (30/group)	Skin (number of tumours/mice at 26 wk): M– Group 1a: 1.9 ± 0.4 Group 1b: 5.9 ± 0.8 Group 1c: 8.6 ± 0.9 F– Group 2a: 3.9 ± 0.6 Group 2b: 3.5 ± 0.6 Group 2c: 3.6 ± 0.6	Group 1b vs 1a, $P < 0.001$ Group 1c vs 1a, $P < 0.0001$	Age, 3 wk Chromium had no effect on growth of the mice. Chromium levels in skin increased with dose Chromium also decreased the time until appearance of first tumours in males

[a] *P*-values for calculated by Poly 3- for NTP studies, which accounts for differential mortality in animals that do not reach terminal sacrifice.
[b] Historical control incidence for 2-yr drinking-water studies with NTP-20000 diet: M: 0/300, F: 0/300.
[c] Historical control incidence for 2-yr drinking-water studies with NTP-20000 diet: M: 2/300, range 0 to 2%; F: 3/300, range 0 to 2%.
[d] Historical control incidence for 2-yr drinking-water studies with NTP-20000 diet: M:11/299, range 0–10%; F: 4/350, range 0 to 4%.
[e] Borneff *et al.* (1968) published in German.
[f] No information on tumour incidence of this group was reported bySedman *et al.* (2006).
[g] Two-Tailed Fisher Exact Test; Authors stated significant but did not provide*P*-value.
[h] Untreated and chromium only, controls not included since no tumours were observed in the study by Davidson*et al.* 2004
bw, body weight; d, day or days; F, female; M, male; mo, month or months; UV, ultraviolet; vs, versus; wk, week or weeks; yr, year or years

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

In humans, the absorption, retention, and elimination of chromium compounds after exposure by inhalation depend on the solubility and particle size of the particular compound inhaled (for an extensive review, see ATSDR, 2008b). The retention may range from several hours to weeks. Inhaled chromium (VI) is readily absorbed from the respiratory tract. The degree of absorption depends on the physical and chemical properties of the particles (size, solubility), and the extent of reduction of the hexavalent form to chromium (III), which is absorbed to a much lesser extent. Thus, after intratracheal instillation in rats, 53–85% of chromium (VI) compounds with a particle size < 5 µm are absorbed into the bloodstream, with higher absorption rates in case of more soluble compounds; the rest remains in the lungs. For comparison, absorption of chromium (III) from the respiratory tract is only 5–30% (ATSDR, 2008b). The same factors mentioned above apply to absorption from the gastrointestinal tract, although absorption by this route is generally much less compared with that in the respiratory tract. Average absorption fractions determined in human volunteers for chromium (III) or chromium (VI) were reported as 0.13% or 6.9%, respectively. Chromium (VI) can penetrate human skin to some extent (ATSDR, 2008b).

In humans and rodents, absorbed chromium (VI) is distributed in nearly all tissues, with the highest concentrations found in the kidney, liver, and bone. Studies conducted by the NTP in male rats and female mice orally exposed to chromium (VI) for 2 years showed dose-related and time-dependent increases in total chromium concentrations in red cells, plasma, and in several organs. The total chromium content of the red cells was higher than that of plasma. The concentration of total chromium in the forestomach was found to be markedly higher in mice than in rats (NTP, 2008).

Within the human body, chromium (VI) undergoes a series of reduction steps to form the thermodynamically stable chromium (III). When reduction occurs extracellularly, this process can be considered as detoxification because the cell membrane is a nearly impermeable barrier for chromium (III). The remaining chromium (VI) is present as a mixture of chromate (CrO_4^{2-}) and hydrochromate ($HCrO_4^-$); because water-soluble chromates are iso-structural with sulfate and phosphate ions, they are readily taken up by sulfate channels. In case of poorly water-soluble chromates, particles of < 5 µm can be phagocytosed, and gradually dissolved intracellularly. Within the cell, chromium (VI) is reduced stepwise to chromium (III), giving rise to reactive intermediates as well as DNA and protein adducts. In blood, chromium (VI) is taken up into red blood cells, is reduced, and then bound to proteins. After exposure by inhalation, excretion occurs predominantly via the urine. Due to the low absorption of chromium compounds from the gastrointestinal tract, the major pathway of elimination after oral exposure is through the faeces (ATSDR, 2008b).

4.2 Genetic and related effects

The oxidation state of chromium is the most important factor when considering its biochemical activity (Beyersmann & Hartwig, 2008; Salnikow & Zhitkovich, 2008). Chromium (VI), but not chromium (III) compounds, have been shown to exert genotoxicity both *in vivo* and *in vitro*.

Lymphocytes of workers exposed to dusts of chromium (VI) compounds showed elevated frequencies of DNA strand breaks (Gambelunghe *et al.*, 2003), sister chromatid exchange (Wu *et al.*, 2001), and micronuclei (Vaglenov *et al.*, 1999; Benova *et al.*, 2002).

After intratracheal instillation in rats, chromium (VI) induced DNA strand breaks in lymphocytes (Gao *et al.*, 1992). After intraperitoneal injection of chromium (VI) to mice, micronuclei were induced in bone marrow. In contrast, no micronucleus induction was observed after oral administration, indicating that chromium (VI) does not reach the target cells to a high extent by this route of exposure (De Flora *et al.*, 2006). Chromium (VI) induces dominant lethal mutations in male mice (Paschin *et al.*, 1982).

In vitro, soluble chromium (VI) compounds are mutagenic in mammalian and bacterial test systems (De Flora *et al.*, 1990).

4.2.1 DNA damage

Chromium (VI) is unreactive towards DNA under physiological conditions. According to the uptake–reduction model originally established by Wetterhahn *et al.* (1989), chromium (VI) undergoes a series of reduction steps in cells, to form the thermodynamically stable chromium (III). Intracellular reduction does not require enzymatic steps but is mediated by direct electron transfer from ascorbate and non-protein thiols, such as glutathione and cysteine. During the reduction process, variable amounts of chromium (V) and chromium (IV) as well as organic radical species are generated; their exact nature, however, depends largely on the reducing species (Wetterhahn & Hamilton, 1989). Furthermore, comparative in-vivo and in-vitro studies revealed a major impact of the intracellular reductants on the nature and biological consequences of the resultant DNA lesions.

The major intracellular reductant under physiological conditions appears to be ascorbate, reaching millimolar concentrations in human tissues, and accounting for about 90% of chromium (VI) reduction reactions *in vivo* (Standeven *et al.*, 1992). In contrast, only micromolar concentrations of ascorbate are usually present in cell cultures (Quievryn *et al.*, 2002), which leads to an increase in thiol-mediated chromate reduction. When ascorbate is the reductant, two electrons are transferred, and chromium (IV) but not chromium (V) is generated as the first intermediate, whereas with cysteine as a reductant, predominantly chromium (V) is formed due to one-electron transfers (Stearns & Wetterhahn, 1994). In both cases, the final product is chromium (III), which reacts to produce different types of DNA lesions.

DNA lesions generated after exposure to chromium (VI) include chromium (III)–DNA adducts, DNA–protein and DNA–DNA interstrand crosslinks, DNA breaks as well as several oxidative DNA–base modifications. The predominant form of chromium (III)–DNA adducts are ternary adducts, where chromium forms a link between DNA and small molecules such as cysteine, histidine, glutathione or ascorbate, presumably arising from preformed chromium–ligand complexes during the reduction process. These adducts are formed primarily at phosphate groups, but the subsequent partial formation of chelates involving the phosphate group and the N^7-position of guanine have been suggested. Chelates formed from chromium–ascorbate particularly are potent premutagenic DNA lesions (Zhitkovich *et al.*, 2001).

The formation of DNA–protein crosslinks after chromate exposure is well established, but is estimated to account for less than 1% of chromium–DNA adducts. Biological consequences are likely to be disturbances of DNA replication and transcription. The formation of DNA–DNA crosslinks appears to be restricted to certain in-vitro conditions, due to severe steric hindrance upon intercalation of octahedral chromium (III) complexes (Zhitkovich, 2005).

DNA single-strand breaks may arise due to the reaction of chromium (V) with hydrogen peroxide, forming hydroxyl radicals. Nevertheless, if ascorbate is the predominant reductant under in-vivo conditions, the generation of chromium (V) and thus, single-strand

breaks, appears to be of minor importance (Quievryn *et al.*, 2003). Cytogenetic alterations in chromium (VI)-exposed cells in culture and *in vivo*, such as increased frequencies of chromosomal breaks and micronuclei, are suggested to be due to DNA double-strand breaks, produced by a cell-replication-dependent mechanism in the G2 phase of the cell cycle. Recent evidence suggests the involvement of mismatch repair in the formation of double-strand breaks. Thus, highly mutagenic ascorbate–chromium–DNA adducts lead to the error-prone repair of double-strand breaks through non-homologous end-joining. Furthermore, they induce mismatches during replication, leading to aberrant mismatch repair. Based on these findings, a model has been created to show that chronic exposure to toxic doses of chromium (VI) provokes the selective outgrowth of mismatch-repair-deficient clones with high rates of spontaneous mutagenesis, and thus, genomic instability (Reynolds *et al.*, 2007; Salnikow & Zhitkovich, 2008). In support of this model, chromium-induced cancers in exposed workers were associated with microsatellite instability and exhibited the loss of expression of MLH1, which is one of the essential mismatch-repair proteins (Takahashi *et al.*, 2005).

4.2.2 Oxidative stress

In the reduction of chromium (VI) to chromium (III) by cellular reductants, potentially toxic intermediates (oxygen radicals, sulfur radicals, and chromium radicals) are generated (Yao *et al.*, 2008). In a cell-free system, chromium (VI) reacted with glutathione to form chromium (V) and thiyl radicals (Wetterhahn *et al.*, 1989). Furthermore, after reduction of chromium (VI) by glutathione, chromium (V) can undergo Fenton-type reactions, producing hydroxyl radicals (Shi *et al.*, 1994), and 8-oxoguanine in isolated DNA (Faux *et al.*, 1992). In cultured mammalian cells, chromium (VI) induced the formation of superoxide and nitric oxide (Hassoun & Stohs, 1995). The administration of chromium (VI) to animals, which have higher tissue levels of ascorbate compared with cultured cells, did not induce the formation of 8-oxoguanine (Yuann *et al.*, 1999). This may be due to the lack of chromium (V) formation when ascorbate is the predominant reducing agent.

4.2.3 Further potentially relevant mechanisms

Besides direct genotoxic effects of chromium (VI) metabolites, chromate may activate various mitogen-activated protein kinases as well as transcription factors involved in inflammation and tumour growth. Nevertheless, because these effects have been observed in cell-culture systems and no distinct effects of chromium (VI) on cell proliferation have been shown, the relevance of these observations remains unclear at present. Perhaps of higher impact are the aneugenic properties of chromium (VI). Chronic treatment with lead-chromate particles induced neoplastic transformation of human bronchial cells, which was accompanied by centrosome amplification, and an increase in aneuploid metaphases (Xie *et al.*, 2007).

4.3 Synthesis

Several mechanisms are involved in the carcinogenesis induced by chromium (VI) that include the induction of DNA damage, the generation of oxidative stress and aneuploidy, leading to cell transformation. With respect to DNA damage, the spectrum of induced lesions appears to depend strongly on the cellular reductant involved. Thus, under physiological conditions with ascorbate as the major reductant, the generation of premutagenic ternary chromium–ascorbate–DNA adducts appears to be of major relevance, which may be linked to the increased number of mismatch-repair-resistant cells observed in chromate-induced lung tumours.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of chromium (VI) compounds. Chromium (VI) compounds cause cancer of the lung.

There is *sufficient evidence* in experimental animals for the carcinogenicity of chromium (VI) compounds.

Chromium (VI) compounds are *carcinogenic to humans (Group 1).*

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NICKEL AND NICKEL COMPOUNDS

Nickel and nickel compounds were considered by previous IARC Working Groups in 1972, 1975, 1979, 1982, 1987, and 1989 (IARC, 1973, 1976, 1979, 1982, 1987, 1990). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Synonyms, trade names, and molecular formulae for nickel, nickel alloys, and selected nickel compounds are presented in Table 1.1. This list is not exhaustive, nor does it necessarily reflect the commercial importance of the various nickel-containing substances, but it is indicative of the range of nickel alloys and compounds available, including some compounds that are important commercially, and those that have been tested in biological systems. Several intermediary compounds occur in refineries that cannot be characterized, and are thus not listed.

1.2 Chemical and physical properties of the agents

Nickel (atomic number, 28; atomic weight, 58.69) is a metal, which belongs to group VIIIB of the periodic table. The most important oxidation state of nickel is +2, although the +3 and +4 oxidation states are also known (Tundermann *et al.*, 2005). Nickel resembles iron, cobalt, and copper in its chemical properties. However, unlike cobalt and iron, it is normally only stable in aqueous solution in the + 2 oxidation state (Kerfoot, 2002). Selected chemical and physical properties for nickel and nickel compounds, including solubility data, were presented in the previous *IARC Monograph* (IARC, 1990), and have been reported elsewhere (ATSDR, 2005).

1.3 Use of the agents

The chemical properties of nickel (i.e. hardness, high melting point, ductility, malleability, somewhat ferromagnetic, fair conductor of heat and electricity) make it suitable to be combined with other elements to form many alloys (NTP, 2000; Tundermann *et al.*, 2005). It imparts such desirable properties as corrosion resistance, heat resistance, hardness, and strength.

Nickel salts are used in electroplating, ceramics, pigments, and as intermediates (e.g. catalysts, formation of other nickel compounds). Sinter nickel oxide is used in nickel catalysts in the ceramics industry, in the manufacture of alloy steel and stainless steel, in the manufacture of nickel salts for specialty ceramics, and in the manufacture of nickel–cadmium (Ni–Cd) batteries, and nickel–metal-hydride batteries. Nickel sulfide is used as a catalyst in

Table 1.1 Chemical names (CAS names are given in italics), synonyms, and molecular formulae or compositions of nickel, nickel alloys and selected nickel compounds

Chemical name	CAS Reg. No.	Synonyms	Formula
Metallic nickel and nickel alloys			
Nickel	7440-02-0	C.I. 77775; Nickel element	Ni
Ferronickel	11133-76-9	*Iron alloy (base), Fe, Ni*; nickel alloy (nonbase) Fe, Ni	Fe, Ni
Nickel aluminium alloys	61431-86-5 37187-84-1	*Raney nickel*; Raney alloy	NiAl
Nickel oxides and hydroxides			
Nickel hydroxide (amorphous)	12054-48-7 (11113-74-9)	Nickel dihydroxide; nickel (II) hydroxide; nickel (2+) hydroxide; *nickel hydroxide (Ni(OH)2)*; nickelous hydroxide	$Ni(OH)_2$
Nickel monoxide	1313-99-1 11099-02-8	Black nickel oxide[a]; green nickel oxide; mononickel oxide; nickel monooxide; nickelous oxide; *nickel oxide (NiO)*; nickel (II) oxide; nickel (2+) oxide	NiO
	34492-97-2	*Bunsenite (NiO)*	
Nickel trioxide	1314-06-3	Black nickel oxide*d*; dinickel trioxide; nickelic oxide; nickel oxide; nickel (III) oxide; *nickel oxide (Ni_2O_3)*; nickel peroxide; nickel sesquioxide	Ni_2O_3
Nickel sulfides			
Nickel disulfide	12035-51-7 12035-50-6	*Nickel sulfide (NiS_2)* *Vaesite (NiS_2)*	NiS_2
Nickel sulfide (amorphous)	16812-54-7 (11113-75-0)	Mononickel monosulfide; nickel mono-sulfide; nickel monosulfide (NiS); nickelous sulfide; nickel (II) sulfide; nickel (2+) sulfide;	NiS
	1314-04-1 (61026-96-8)	*Nickel sulfide (NiS)* *Millerite (NiS)*	
Nickel subsulfide	12035-72-2	Nickel sesquisulfide; nickel subsulfide (Ni_3S_2); *nickel sulfide (Ni_3S_2)*; trinickel disulfide	Ni_3S_2
	12035-71-1	*Heazlewoodite (Ni_3S_2)*; Khizlevudite	
Pentlandite	53809-86-2 12174-14-0	Pentlandite ($Fe_9Ni_9S_{16}$) Pentlandite	Fe9Ni9S16 $(Fe_{0.4-0.6}Ni_{0.4-0.6})_9S_8$

Table 1.1 (continued)

Chemical name	CAS Reg. No.	Synonyms	Formula
Nickel salts			
Nickel carbonate	3333-67-3	*Carbonic acid, nickel (2+) salt (1:1)*; nickel carbonate (1:1); nickel (II) carbonate; nickel (2+) carbonate; nickel carbonate ($NiCO_3$); nickel (2+) carbonate ($NiCO_3$); nickel monocarbonate; nickelous carbonate	$NiCO_3$
Basic nickel carbonates	12607-70-4	Carbonic acid, nickel salt, basic; nickel carbonate hydroxide ($Ni_3(CO_3)(OH)_4$); *nickel, (carbonato(2-)) tetrahydroxytri-*	$NiCO_3.2Ni(OH)_2$
	12122-15-5	*Nickel bis(carbonato(2-)) hexahydroxypenta-*; nickel hydroxycarbonate	$2NiCO_3.3Ni(OH)_2$
Nickel acetate	373-02-4	*Acetic acid, nickel (2+) salt*; nickel (II) acetate; nickel (2+) acetate; nickel diacetate; nickelous acetate	$Ni(OCOCH_3)_2$
Nickel acetate tetrahydrate	6018-89-9	*Acetic acid, nickel (+2) salt, tetrahydrate*	$Ni(OCOCH_3)_2.4H_2O$
Nickel ammonium sulfates	15-699-18-0	Ammonium nickel sulfate ($(NH_4)_2Ni(SO_4)_2$); nickel ammonium sulfate ($Ni(NH_4)_2(SO_4)_2$); *sulfuric acid, ammonium nickel (2+) salt (2:2:1)*	$Ni(NH_4)_2(SO_4)_2$
Nickel ammonium sulfate hexahydrate	25749-08-0	Ammonium nickel sulfate ($(NH_4)_2Ni_2(SO_4)_3$); *sulfuric acid, ammonium nickel (2+) salt (3:2:2)*	$Ni_2(NH_4)_2(SO_4)_3$
	7785-20-8	Ammonium nickel (2+) sulfate hexahydrate; ammonium nickel sulfate ($(NH_4)_2Ni(SO_4)_2$); diammonium nickel disulfate hexahydrate; diammonium nickel (2+) disulfate hexahydrate; nickel ammonium sulfate ($Ni(NH_4)_2(SO_4)_2$) hexahydrate; nickel diammonium disulfate hexahydrate; *sulfuric acid, ammonium nickel (2+) salt (2:2:1), hexahydrate*	$Ni(NH_4)_2(SO_4)_2.6H_2O$
Nickel chromate	14721-18-7	*Chromium nickel oxide ($NiCrO_4$)*; nickel chromate ($NiCrO_4$); nickel chromium oxide ($NiCrO_4$)	$NiCrO_4$
Nickel chloride	7718-54-9	Nickel (II) chloride; nickel (2+) chloride; *nickel chloride ($NiCl_2$)*; nickel dichloride; nickel dichloride ($NiCl_2$); nickelous cholride	$NiCl_2$
Nickel chloride hexahydrate	7791-20-0	*Nickel chloride (NiCl2) hexahydrate*	$NiCl_2.6H_2O$
Nickel nitrate hexahydrate	13478-00-7	Nickel (2+) bis(nitrate)hexahydrate; nickel dinitrate hexahydrate; nickel (II) nitrate hexahydrate; nickel nitrate (Ni(NO3)2) hexahydrate; nickelous nitrate hexahydrate; *nitric acid, nickel (2+) salt, hexahydrate*	$Ni(NO_3)_2.6H_2O$
Nickel sulfate	7786-81-4	Nickel monosulfate; nickelous sulfate; nickel sulfate (1:1); nickel (II) sulfate; nickel (2+) sulfate; nickel (2+) sulfate (1:1); nickel sulfate ($NiSO_4$); *sulfuric acid, nickel (2+) salt (1:1)*	$NiSO_4$
Nickel sulfate hexahydrate	10101-97-0	*Sulfuric acid, nickel (2+) salt (1:1), hexahydrate*	$NiSO_4.6H_2O$
Nickel sulfate heptahydrate	10101-98-1	*Sulfuric acid, nickel (2+) salt (1:1), heptahydrate*	$NiSO_4.7H_20$

Table 1.1 (continued)

Chemical name	CAS Reg. No.	Synonyms	Formula
Other nickel compounds			
Nickel carbonyl	13463-39-3	*Nickel carbonyl ($Ni(CO)_4$), (T-4)-*; nickel tetracarbonyl; tetracarbonylnickel; tetracarbonylnickel (0)	$Ni(CO)_4$
Nickel antimonide	12035-52-8	*Antimony compound with nickel (1:1)*; nickel antimonide (NiSb); nickel compound with antimony (1:1); nickel monoantimonide	NiSb
	12125-61-0	*Breithauptite (SbNi)*	
Nickel arsenides	27016-75-7	*Nickel arsenide (NiAs)*	NiAs
	1303-13-5	Nickeline; *nickeline (NiAs)*; niccolite	NiAs
	12256-33-6	*Nickel arsenide ($Ni_{11}As_8$)*; nickel arsenide tetragonal	$Ni_{11}As_8$
	12044-65-4	*Maucherite ($Ni_{11}As_8$)*; Placodine; Temiskamite	$Ni_{11}As_8$
	12255-80-0	*Nickel arsenide (Ni_5As_2)*; nickel arsenide hexagonal	Ni_5As_2
Nickel selenide	1314-05-2 12201-85-3	Nickel monoselenide; *nickel selenide (NiSe)* Maekinenite; *Makinenite (NiSe)*	NiSe
Nickel subselenide	12137-13-2	*Nickel selenide (Ni_3Se_2)*	Ni_3Se_2
Nickel sulfarsenide	12255-10-6 12255-11-7	*Nickel arsenide sulfide (NiAsS)* *Gersdorffite (NiAsS)*	NiAsS
Nickel telluride	12142-88-0 24270-51-7	Nickel monotelluride; *nickel telluride (NiTe)* *Imgreite (NiTe)*	NiTe
Nickel titanate	12035-39-1	Nickel titanate(IV); nickel titanate (Ni-TiO3); *nickel titanium oxide (NiTiO3)*; nickel titanium trioxide	$NiTiO_3$
Chrome iron nickel black spinel	71631-15-7	CI: 77 504; *CI Pigment Black 30*; nickel iron chromite black spinel	$(Ni,Fe)(CrFe)_2O_4$ NS
Nickel ferrite brown spinel	68187-10-0	*CI Pigment Brown 34*	$NiFe_2O_4$
Nickelocene	1271-28-9	Bis(η5-2,4-cyclopentadien-1-yl)nickel; di-π-cyclopentadienylnickel; dicyclopentadienyl-nickel; bis(η5-2,4-cyclopentadien-1-yl)-nickel	π-(C5H5)2Ni

[a] In commercial usage, 'black nickel oxide' usually refers to the low-temperature crystalline form of nickel monoxide, but nickel trioxide (Ni_2O_3), an unstable oxide of nickel, may also be called 'black nickel oxide'.

the petrochemical industry or as an intermediate in the metallurgical industry.

According to the US Geological Survey, world use of primary nickel in 2006 was 1.40 million tonnes, a 12% increase over 2005. Stainless steel manufacture accounted for more than 60% of primary nickel consumption in 2006 (USGS, 2008). Of the 231000 tonnes of primary nickel consumed in the USA in 2007, approximately 52% was used in stainless and alloy steel production, 34% in non-ferrous alloys and superalloys, 10% in electroplating, and 4% in other uses. End uses of nickel in the USA in 2007 were as follows: transportation, 30%; chemical industry, 15%; electrical equipment, 10%; construction, 9%; fabricated metal products, 8%; household appliances, 8%; petroleum industry, 7%; machinery, 6%; and others, 7% (Kuck, 2008).

1.3.1 Metallic nickel and nickel alloys

Pure nickel metal is used to prepare nickel alloys (including steels). It is used as such for plating, electroforming, coinage, electrical components, tanks, catalysts, battery plates, sintered components, magnets, and welding rods. Ferronickel is used to prepare steels. Stainless and heat-resistant steels accounted for 93% of its end-use in 1986. Nickel-containing steels with low nickel content (< 5%) are used in construction and tool fabrication. Stainless steels are used in general engineering equipment, chemical equipment, domestic applications, hospital equipment, food processing, architectural panels and fasteners, pollution-control equipment, cryogenic uses, automotive parts, and engine components (IARC, 1990).

Nickel alloys are often divided into categories depending on the primary metal with which they are alloyed (e.g. iron, copper, molybdenum, chromium) and their nickel content. Nickel is alloyed with iron to produce alloy steels (containing 0.3–5% nickel), stainless steels (containing as much as 25–30% nickel, although 8–10% nickel is more typical), and cast irons. Nickel–copper alloys (e.g. Monel alloys) are used for coinage (25% nickel, 75% copper), industrial plumbing (e.g. piping and valves), marine equipment, petrochemical equipment, heat exchangers, condenser tubes, pumps, electrodes for welding, architectural trim, thermocouples, desalination plants, ship propellers, etc. Nickel–chromium alloys (e.g. Nichrome) are used in many applications that require resistance to high temperatures such as heating elements, furnaces, jet engine parts, and reaction vessels. Molybdenum-containing nickel alloys and nickel–iron–chromium alloys (e.g. Inconel) provide strength and corrosion resistance over a wide temperature range, and are used in nuclear and fossil-fuel steam generators, food-processing equipment, and chemical-processing and heat-treating equipment. Hastelloy alloys (which contain nickel, chromium, iron, and molybdenum) provide oxidation and corrosion resistance for use with acids and salts. Nickel-based super-alloys provide high-temperature strength and creep, and stress resistance for use in gas-turbine engines (ATSDR, 2005).

Other groups of nickel alloys are used according to their specific properties for acid-resistant equipment, heating elements for furnaces, low-expansion alloys, cryogenic uses, storage of liquefied gases, high-magnetic-permeability alloys, and surgical implant prostheses.

1.3.2 Nickel oxides and hydroxides

The nickel oxide sinters are used in the manufacture of alloy steels and stainless steels.

Green nickel oxide is a finely divided, relatively pure form of nickel monoxide, produced by firing a mixture of nickel powder and water in air at 1000 °C (IARC, 1990). It is used to manufacture nickel catalysts and specialty ceramics (for porcelain enamelling of steel; in the manufacture of magnetic nickel-zinc ferrites used in electric motors, antennas and television tube yokes; and

as a colourant in glass and ceramic stains used in ceramic tiles, dishes, pottery, and sanitary ware).

Black nickel oxide is a finely divided, pure nickel monoxide, produced by calcination of nickel hydroxycarbonate or nickel nitrate at 600 °C; nickel trioxide (Ni_2O_3), an unstable oxide of nickel, may also be called 'black nickel oxide' (IARC, 1990). Black nickel oxide is used in the manufacture of nickel salts, specialty ceramics, and nickel catalysts (e.g. to enhance the activity of three-way catalysts containing rhodium, platinum, and palladium used in automobile exhaust control).

Nickel hydroxide is used as a catalyst intermediate, and in the manufacture of Ni–Cd batteries (Antonsen & Meshri, 2005).

1.3.3 Nickel sulfides

Nickel sulfide is used as a catalyst in petrochemical hydrogenation when high concentrations of sulfur are present in the distillates. The major use of nickel monosulfide is as an intermediate in the hydrometallurgical processing of silicate-oxide nickel ores (IARC, 1990). Nickel subsulfide is used as an intermediate in the primary nickel industry (ATSDR, 2005).

1.3.4 Nickel salts

Nickel acetate is used in electroplating, as an intermediate (e.g. as catalysts and in the formation of other nickel compounds), as a dye mordant, and as a sealer for anodized aluminium.

Nickel carbonate is used in the manufacture of nickel catalysts, pigments, and other nickel compounds (e.g. nickel oxide, nickel powder); in the preparation of coloured glass; and, as a neutralizing compound in nickel-electroplating solutions.

Nickel ammonium sulfate is used as a dye mordant, in metal-finishing compositions, and as an electrolyte for electroplating.

Nickel chloride is used as an intermediate in the manufacture of nickel catalysts, and to absorb ammonia in industrial gas masks.

Nickel nitrate hexahydrate is used as an intermediate in the manufacture of nickel catalysts and Ni–Cd batteries.

Nickel sulfate hexahydrate is used in nickel electroplating and nickel electrorefining, in 'electroless' nickel plating, and as an intermediate (in the manufacture of other nickel chemicals and catalysts) (Antonsen & Meshri, 2005).

1.3.5 Other nickel compounds

The primary use for nickel carbonyl is as an intermediate (in the production of highly pure nickel), as a catalyst in chemical synthesis, as a reactant in carbonylation reactions, in the vapour-plating of nickel, and in the fabrication of nickel and nickel alloy components and shapes.

Nickelocene is used as a catalyst and complexing agent, and nickel titanate is used as a pigment (Antonsen & Meshri, 2005).

No information was available to the Working Group on the use of nickel selenides or potassium nickelocyanate.

1.4 Environmental occurrence

Nickel and its compounds are naturally present in the earth's crust, and are emitted to the atmosphere via natural sources (such as windblown dust, volcanic eruptions, vegetation forest fires, and meteoric dust) as well as from anthropogenic activities (e.g. mining, smelting, refining, manufacture of stainless steel and other nickel-containing alloys, fossil fuel combustion, and waste incineration). Estimates for the emission of nickel into the atmosphere from natural sources range from 8.5 million kg/year in the 1980s to 30 million kg/year in the early 1990s (ATSDR, 2005). The general population is exposed to low levels of nickel in ambient air, water, food, and through tobacco consumption.

1.4.1 Natural occurrence

Nickel is widely distributed in nature and is found in animals, plants, and soil (EVM, 2002). It is the 24th most abundant element, forming about 0.008% of the earth's crust (0.01% in igneous rocks). The concentration of nickel in soil is approximately 79 ppm, with a range of 4–80 ppm (EVM, 2002; ATSDR, 2005).

1.4.2 Air

Nickel is emitted to the atmosphere from both natural and anthropogenic sources. It has been estimated that approximately 30000 tonnes of nickel may be emitted per year to the atmosphere from natural sources. The anthropogenic emission rate is estimated to be between 1.4–1.8 times higher than the natural emission rate.

The two main natural sources are volcanoes and windblown dust from rocks and soil, estimated to respectively contribute 14000 tonnes/year and 11000 tonnes/year (NTP, 2000; Barbante *et al.*, 2002). Other relatively minor sources include: wild forest fires (2300 tonnes/year), sea salt spray (1300 tonnes/year), continental particulates (510 tonnes/year), marine (120 tonnes/year), and continental volatiles (100 tonnes/year) (Barbante *et al.*, 2002).

Anthropogenic activities release nickel to the atmosphere, mainly in the form of aerosols (ATSDR, 2005). Fossil fuel combustion is reported to be the major contributor of atmospheric nickel in Europe and the world, accounting for 62% of anthropogenic emissions in the 1980s (Barbante *et al.*, 2002; ATSDR, 2005). In 1999, an estimated 570000 tons of nickel were released from the combustion of fossil fuels worldwide (Rydh & Svärd, 2003). Of this, 326 tons were released from electric utilities (Leikauf, 2002). Of the other anthropogenic sources, nickel metal and refining accounted for 17% of total emissions, municipal incineration 12%, steel production 3%, other nickel-containing alloy production 2%, and coal combustion 2% (ATSDR, 2005).

Atmospheric nickel concentrations are higher in rural and urban air (concentration range: 5–35 ng/m^3) than in remote areas (concentration range: 1–3 ng/m^3) (WHO, 2007).

1.4.3 Water

Particulate nickel enters the aquatic environment from a variety of natural and anthropogenic sources. Natural sources include the weathering and dissolution of nickel-containing rocks and soil, disturbed soil, and atmospheric deposition. Anthropogenic sources include: industrial processes (e.g. mining and smelting operations), industrial waste water and effluent (e.g. tailings piles run-off), domestic waste water, and landfill leachate (NTP, 2000; ATSDR, 2005; WHO, 2007). Several factors influence the concentration of nickel in groundwater and surface water including: soil use, pH, and depth of sampling (WHO, 2007). Most nickel compounds are relatively water soluble at low pH (i.e. pH < 6.5). As a result, acid rain tends to increase the mobility of nickel in soil, which, in turn, has a corresponding impact on nickel concentrations in groundwater (NTP, 2000; WHO, 2007).

Based on measurement data from the 1980s, the following average nickel concentrations have been reported for groundwater, seawater and surface water, respectively: < 20 µg/L, 0.1–0.5 µg/L, and 15–20 µg/L (NTP, 2000; ATSDR, 2005). Nickel concentrations as high as 980 µg/L have been measured in groundwater with pH < 6.2 (WHO, 2007). Levels of dissolved nickel ranging from < 1–87 µg/L have been reported in urban storm run-off water samples (ATSDR, 2005).

Nickel concentrations in the range of 6–700 pg/g have been measured in high-altitude snow and ice near the summit of Mont Blanc on the French-Italian border. Seasonal variations were observed, with higher concentrations in the summer layers than in the winter layers.

Nickel levels appeared to be more associated with anthropogenic inputs (e.g. oil combustion from power generation, automobile and truck traffic) than with natural sources, such as rock and soil dust (Barbante *et al.*, 2002).

1.4.4 Soil and sediments

Natural and anthropogenic sources (e.g. mining and smelting, coal fly ash, bottom ash, metal manufacturing waste, commercial waste, atmospheric fall-out and deposition, urban refuse, and sewage sludge) contribute to the levels of nickel found in soil and sediments (NTP, 2000; ATSDR, 2005). Of the nickel emitted to the environment, the largest releases are to the soil. In 2002, estimated releases of nickel and nickel compounds from manufacturing and processing facilities (required to report to the US Toxic Release Inventory Program) were approximately 5530 and 14800 metric tonnes, respectively—accounting for 82% and 87% of estimated total nickel releases to the environment (ATSDR, 2005).

In a study of urban soil quality, a harmonized sampling regime was used to compare concentrations of nickel in six European cities differing markedly in their climate and industrial history. The sites were as far as possible from current point sources of pollution, such as industrial emissions, but all were bordered by major roads, and are thus likely to have been affected by vehicle emissions. To assess the vertical distribution of soil parameters, two depths were sampled at each point: a surface sample at 0–10 cm and a subsurface sample at 10–20 cm. The surface sample mean nickel concentration was in the range of 11–207 mg /kg, and the corresponding mean concentration in the subsurface sample, 10–210 mg/kg (Madrid *et al.*, 2006).

1.5 Human exposure

1.5.1 Exposure of the general population

Ingestion of nickel in food, and to a lesser degree in drinking-water, is the primary route of exposure for the non-smoking general population. Exposure may also occur via inhalation of ambient air and percutaneous absorption (NTP, 2000; ATSDR, 2005; WHO, 2007). The daily intake of nickel from food and beverages varies by foodstuff, by country, by age, and by gender (EVM, 2002; ATSDR, 2005). Data from a study in the USA give estimates of daily dietary intakes in the range of 101–162 µg/day for adults, 136–140 µg/day for males, and 107–109 µg/day for females. Estimates for pregnant and lactating women are higher with average daily intakes of 121 µg/day and 162 µg/day, respectively (ATSDR, 2005). Based on the concordance between different studies of dietary intake, diet is reported to contribute less than 0.2 mg/day (WHO, 2007).

Inhalation of nickel from ambient air is generally a minor route of exposure for the general population. The following daily intakes of nickel have been estimated: less than 0.05 µg/day in the USA; 0.42 µg/day (mean ambient concentration) and 15 µg/day (highest ambient concentration) in the Sudbury basin region in Ontario, Canada; and, 122 µg/day (based on the highest ambient reported nickel concentration) in the Copper Cliff region of Ontario, Canada. These estimates are based on a breathing rate of 20 m^3/day, and nickel concentrations of 2.2 ng/m^3, 21 ng/m^3, 732 ng/m^3, and 6100 ng/m^3, respectively (ATSDR, 2005).

1.5.2 Occupational exposure

Nickel, in the form of various alloys and compounds, has been in widespread commercial use for over 100 years. Several million workers worldwide are exposed to airborne fumes, dusts and mists containing nickel and its compounds. Exposures by inhalation, ingestion or skin

contact occur in nickel-producing industries (e.g. mining, milling, smelting, and refining), as well as in nickel-using industries and operations (e.g. alloy and stainless steel manufacture; electroplating and electrowinning; welding, grinding and cutting). Insoluble nickel is the predominant exposure in nickel-producing industries, whereas soluble nickel is the predominant exposure in the nickel-using industries. Occupational exposure results in elevated levels of nickel in blood, urine and body tissues, with inhalation as the main route of uptake (IARC, 1990; NTP, 2000).

Estimates of the number of workers potentially exposed to nickel and nickel compounds have been developed by the National Institute of Occupational Safety and Health (NIOSH) in the USA and by CAREX (CARcinogen EXposure) in Europe. Based on the National Occupation Exposure Survey (NOES), conducted during 1981–1983, NIOSH estimated that 507681 workers, including 19673 female workers, were potentially exposed to 'Ni, Nickel-MF Unknown' (agent code: 50420) in the workplace (NIOSH, 1990). The following six industries accounted for nearly 60% of exposed workers: 'fabricated metal products' (n = 69984), 'special trade contractors' (n = 55178), 'machinery, except electrical' (n = 55064), 'transportation equipment' (n = 44838), 'primary metal industries' (n = 39467), and 'auto repair, services, and garages' (n = 27686). Based on occupational exposure to known and suspected carcinogens collected during 1990–1993, the CAREX database estimates that 547396 workers were exposed to nickel and nickel compounds in the European Union. Over 83% of these workers were employed in the 'manufacture of fabricated metal products, except machinery and equipment' (n = 195597), 'manufacture of machinery, except electrical' (n = 122985), 'manufacture of transport equipment' (n = 64720), 'non-ferrous base metal industries' (n = 32168), 'iron and steel basic industries' (n = 26504), and 'metal ore mining' (n = 16459). CAREX Canada (2011) estimates that approximately 50000 Canadians are exposed to nickel in the workplace (95% male). Exposed industries include: commercial/industrial machinery and equipment repair/maintenance; architectural, structural metals manufacturing; specialty trade contractors; boiler, tank and shipping container manufacturing; metal ore mining; motor vehicle parts manufacturing; machine shops, turned product, screw, nut and bolt manufacturing; coating, engraving, heat treating and allied activities; iron/steel mills and ferro-alloy manufacturing; non-ferrous metal production and processing.

Historically, metallic nickel exposures tended to be higher in nickel-producing industries than in the nickel-using industries, with estimates of historical mean levels of exposure to inhalable metallic nickel in the range of 0.01–6.0 mg/m^3 and 0.05–0.3 mg /m^3, respectively. However, data from the EU suggest that occasional higher exposures to inhalable metallic nickel may be present in certain industry sectors (Sivulka, 2005).

Data on early occupational exposures to nickel and nickel compounds were summarized in the previous *IARC Monograph* (IARC, 1990). Data from studies and reviews on nickel exposure published since the previous *IARC Monograph* are summarized below for both the nickel-producing and the nickel-using industries.

(a) Studies of nickel-producing industries

Ulrich *et al.* (1991) collected data on several indicators of nickel exposure (stationary and personal air sampling; urinary nickel excretion) among electrolytic nickel production workers in the Czech Republic (formerly, Czechoslovakia). Air samples (n = 52) were collected on membrane filters and analysed by electrothermal atomic absorption spectrometry. Urine samples (n = 140) were collected during the last 4 hours of workers' shifts, and the results were corrected to a standard density of 1.024. In a matched-pair analysis of air and urine samples collected from 18 electrolysis workers, the correlation coefficient

was 0.562; the mean concentration of nickel in urine was 53.3 μg/L (range, 1.73–98.55 μg/L), and the mean concentration in air was 0.187 mg/m³ (range, 0.002–0.481 mg/m³).

In a study conducted at a Finnish electrolytic nickel refinery, Kiilunen *et al.* (1997) collected data on nickel concentrations in air, blood, and urine. Stationary samples ($n = 141$) were collected from 50 locations in the refinery, including those areas where breathing zone samples were taken. Personal (i.e. 8-hour breathing zone) samples were collected over 4 successive work days ($n = 157$), from the shoulders when no respiratory protection was worn, inside the mask when protective equipment was worn, and inside the mask hanging on the shoulder of the worker when the mask was taken off. Historical occupational hygiene measurements were examined to assess past exposure. Spot urine samples ($n = 154$) were collected, pre- and post-shift, over 4 successive work days and 1 free day thereafter. Blood samples ($n = 64$) were collected at the beginning of the study and at the end of the last work shift. A total of 34 workers (of 100) volunteered to participate in the study. Urinary nickel results in the workers were compared with two non-exposed control groups (30 office workers from the refinery and 32 unexposed persons from the Helsinki area). For the stationary samples, nickel concentrations were reported by location as water-soluble nickel, acid-soluble nickel and total nickel (all in μg/m³). Geometric mean nickel concentrations ranged from: 7.4 μg/m³ ('other sites') to 451 μg/m³ (in 'tank house 3′) for water-soluble nickel; 0.5 μg/m³ ('other sites') to 4.6 μg/m³ ('solution purification') for acid-soluble nickel; and, 7.6 μg/m³ ('other sites') to 452 μg/m³ (in 'tank house 3′). For the breathing zone samples, the range of geometric mean nickel concentrations was 0.2–3.2 μg/m³ (inside the mask) and 0.6–63.2 μg/m³ (no mask). Based on a review of historical stationary sampling data, average nickel concentrations varied in the range of 230–800 μg/m³ over the period 1966–88. Lower concentrations (112–484 μg/m³) were observed in the early 1990s. Geometric mean after-shift urinary concentrations of nickel were in the range of 0.1–0.8 μmol/L (mask in use) and 0.5–1.7 μmol/L (no mask in use). Urinary nickel concentrations were still elevated after 2- and 4-week vacations. No consistent correlations between airborne nickel concentrations and nickel concentrations in the blood or urine were observed.

Thomassen *et al.* (2004) measured the exposure of 135 copper refinery workers (45 females, 90 males) to copper, nickel and other trace elements at a nickel refinery complex in Monchegorsk, the Russian Federation. Full-shift breathing zone samples were collected for workers in the pyrometallurgical process ($n = 138$) and in the electrorefining process ($n = 123$) areas. Workers wore personal samplers for two to four full shifts. IOM samplers were used to assess the inhalable aerosol fraction, and Respicon samplers (3-stage virtual impactors) were used to separate the inhalable fraction into respirable, tracheobronchal, and extrathoracic aerosol fractions. The geometric mean inhalable nickel concentration was in the range of 0.024–0.14 mg/m³ for samples taken in the pyrometallurgical areas, and 0.018–0.060 mg/m³ for samples taken in the electrorefining areas (data presented as the sum of the inhalable water-soluble and water-insoluble subfractions). For the inhalable aerosol nickel concentrations observed in the pyrometallurgical process steps, the water-insoluble subfraction contained higher levels than the water-soluble fraction, with geometric means of 59 μg/m³ and 14 μg/m³, respectively. In the electrorefining process area, the nickel concentrations in the inhalable subfractions were 14 μg/m³ (water-soluble) and 10 μg/m³ (water-insoluble).

Air monitoring was conducted in three areas of a nickel base metal refinery in South Africa (the ball mill area, the copper winning area, and the nickel handling area). Personal breathing zone samples ($n = 30$) were collected in all areas of the

plant, and were analysed gravimetrically and by inductively coupled plasma mass spectroscopy. The mean time-weighted average concentrations for soluble, insoluble and total nickel dust, respectively, were 44, 51, and 95 μg/m^3 in the ball mill area; 395, 400, and 795 μg/m^3 in the nickel handling area; and 46, 17, and 63 μg/m^3 in the copper winning area (Harmse & Engelbrecht, 2007).

Airborne dust concentrations, nickel concentrations, nickel speciation, and aerosol particle size distributions in two large-scale nickel production facilities were assessed by collecting a total of 46 inhalable samples (30 personal, 16 area), and 28 cascade impactor samples (18 personal, 10 area). Samples were collected using IOM and Marple cascade impactor sampling heads, and analysed gravimetrically. At the first site, inhalable concentrations were in the range of 0.5–9.1 mg/m^3 for the personal samples, and 0.2–5.7 mg/m^3 for the area samples (median concentrations, 0.7 mg/m^3 and 0.4 mg/m^3, respectively). Total nickel levels in the personal samples were in the range of 1.8–814.9 μg/m^3, and 19.8–2481.6 μg/m^3 in the area samples (median concentrations, 24.6 μg/m^3 and 92.0 μg/m^3, respectively). At the second site, airborne concentrations of inhalable dust were in the range of 1.2–25.2 mg/m^3 for the personal samples, and 1.5–14.3 mg/m^3 (median concentrations, 3.8 mg/m^3 and 2.9 mg/m^3, respectively) for the area samples. Total nickel levels were in the range of 36.6–203.4 μg/m^3 in the area samples, and 0.2–170.7 μg/m^3 in the personal samples (median concentrations, 91.3 and 15.2 μg/m^3, respectively) (Creely & Aitken, 2008).

(b) Studies of nickel-using industries

Bavazzano *et al.* (1994) collected air, face, hand, and spot urine samples from 41 male workers in electroplating operations in 25 small factories in the province of Florence, Italy, and compared them to samples collected from non-exposed male subjects (face and hand samples: n = 15 subjects aged 15–60 years old; urine samples: n = 60 subjects aged 22–63 years old). For the airborne nickel measurements, personal exposure were in the range of 0.10–42 μg/m^3 (median concentration, 2.3 μg/m^3). The median nickel levels in the urine, on the hands, and on the face were, respectively, 4.2 μg/L (range, 0.7–50 μg/L), 39 μg (range, 1.9–547 μg), and 9.0 μg (range, 1.0–86 μg). Median hand, face, and urine nickel levels for the control subjects were, respectively, 0.8 μg (range, 0.0–5.3 μg; n = 15), 0.30 μg (range, 0.0–2.4; n = 15), and 0.7 μg (range, 0.1–2.5 μg; n = 60).

In an occupational hygiene survey of 38 nickel electroplating shops in Finland, exposure to nickel was assessed by questionnaire (n = 163), urine samples (phase 1: n = 145; phase 2: n = 104), bulk samples (n = 30), and air measurements in three representative shops (one clean, one intermediate, one dirty) on 1 day during which urine samples were also being collected. Full-shift breathing zone samples were collected from inside and outside a respirator with filters. In the first phase of the study, average urinary nickel concentration was 0.16 μmol/L (range, 0.0–5.0 μmol/L; n = 145). The range of mean values for different workplaces was 0.01–0.89 μmol/L, and for the median values, 0.02–0.05 μmol/L. For the 97 workers followed in the second phase, urinary nickel concentrations were observed to fluctuate with exposure, with mean nickel concentrations in the range of 0.10–0.11 μmol/L for the morning specimens, and 0.12–0.16 μmol/L for the afternoon specimens. Personal breathing zone nickel concentrations were as follows: 0.5 μg/m^3 (hanger worker in the 'clean shop'), 0.7 μg/m^3 (worker responsible for maintenance of nickel bath in the 'clean' shop), and in the range of 5.6–78.3 μg/m^3 for workers (n = 6) in the 'dirty' shop. In the area samples, nickel concentrations were 26 μg/m^3 (near the nickel bath in the 'clean' shop), 11.9–17.8 μg/m^3 (in the hanging area of the 'dirty' shop), and 73.3 μg/m^3 (beside the nickel bath in the 'dirty' shop) (Kiilunen *et al.*, 1997).

Kiilunen (1997) analysed data from the biomonitoring registry and the occupational hygiene service registry of the Finnish Institute of Occupational Health to examine trends in nickel exposure during 1980–89. A total of 1795 urinary nickel samples (for which it was possible to identify job titles) were examined, along with 260 nickel measurements from the breathing zone of workers for whom job titles were available. Across all job titles, the ranges of mean urinary nickel concentrations, by time period, were as follows: 0.05–0.52 µmol/L for 1980–82, 0.14–0.51 µmol/L for 1983–85, and 0.17–0.87 µmol/L for 1986–89. The two largest occupational groups sampled were platers (*n* = 503), and welders (*n* = 463). Mean urinary concentrations for platers, by time period, were 0.35 µmol/L for 1980–82 (range, 0.01–2.95), 0.30 µmol/L for 1983–85 (range, 0.01–2.10), and 0.38 µmol/L for 1986–89 (range, 0.03–2.37). Mean urinary concentrations for welders, by time period, were 0.22 µmol/L for 1980–82 (range, 0.03–1.58), 0.17 µmol/L for 1983–85 (range, 0.03–0.65), and 0.21 µmol/L for 1986–89 (range, 0.01–1.58). Analysis of the breathing zone measurements revealed that 22.1% of all measurements in 1980–82 had exceeded the occupational exposure limit (OEL) of 0.1 mg/m^3. Similar results were seen for the 1983–85 period (24.8%), rising to 30.7% for the 1986–89 period. Job titles with mean values over the OEL in 1983–85 included: grinders (mean, 0.76 mg/m^3, *n* = 29), one metal worker (0.12 mg/m^3), powder cutters (mean, 0.34 mg/m^3, *n* = 31), one spray painter (0.20 mg/m^3), and welders (0.17 mg/m^3, *n* = 72). Mean levels exceeded the OEL in the following four occupational groups during 1986–89: carbon arc chisellers (mean, 0.6 mg/m^3, *n* = 2), grinders (mean, 0.28 mg/m^3, *n* = 19), one warm handler (0.18 mg/m^3), and burn cutters (mean, 0.14 mg/m^3, *n* = 2).

The association between occupational exposure to airborne nickel and nickel absorption was examined by collecting personal breathing zone samples and urine samples from 10 workers at a galvanizing plant in Brazil that uses nickel sulfate. Spot urine samples were collected pre- and post-shift from the nickel-exposed workers over 5 consecutive days, and from 10 non-nickel exposed workers employed at a zinc plant over 3 consecutive days (*n* = 97 and 55, respectively). Both groups completed a questionnaire on occupational history, health and lifestyle factors; exposed workers also underwent a medical examination. Personal breathing zone samples (first 4 hours of shift) were collected using NIOSH protocols. Geometric mean airborne nickel levels were in the range of 2.8–116.7 µg/m^3, and the urine levels, from samples taken post-shift, were in the range of 4.5–43.2 µg/g creatinine (mean, 14.7 µg/g creatinine) (Oliveira *et al.*, 2000dddd.

Sorahan (2004) examined data on mean (unadjusted) levels of exposure to inhalable nickel at a nickel alloy plant during 1975–2001 in Hereford, the United Kingdom. Data were reported for two time periods: 1975–80 and 1997–2001. Mean nickel levels (unadjusted) for the earlier period were as follows: 0.84 mg/m^3 in the melting, fettling, and pickling areas; 0.53 mg/m^3 in the extrusion and forge, hot strip and rolling, engineering, and melting stores areas; 0.55 mg/m^3 in the machining, hot rolling, Nimonic finishing, and craft apprentice areas; 0.40 mg/m^3 in the roll turning and grinding, cold rolling, cold drawing, wire drawing, and inspection areas; and 0.04 mg/m^3 in the process stock handling, distribution and warehouse areas. The corresponding mean nickel levels (unadjusted) for the latter period were: 0.37 mg/m^3, 0.45 mg/m^3, 0.31 mg/m^3, 0.30 mg/m^3, and 0.29 mg/m^3, respectively.

Eight-hour TWA (8-h TWA) exposures calculated for the period 1997–2001 were 0.33 mg/m^3, 0.31 mg/m^3, 0.16 mg/m^3, 0.16 mg/m^3, and 0.27 mg/m^3, respectively.

Sorahan & Williams (2005) assessed the mortality of workers at a nickel carbonyl refinery in Clydach, the United Kingdom to determine whether occupational exposure to nickel resulted in increased risks of nasal cancer and lung cancer.

Using personal sampling data collected in the 1980s and 1990s, 8-h TWA exposure to total inhalable nickel was calculated, and assigned to six categories of work, based on the predominant species of nickel exposure. The six categories of work were: feed handling and nickel extraction, including kilns (oxide/metallic); pellet and powder production, and shipping (metallic); nickel salts and derivatives, and effluent (metallic/soluble); wet treatment and related processes (metallic/subsulfide/soluble); gas plant (non-nickel); and engineering and site-wide activities that could include any of the preceding work areas. Mean levels of total inhalable nickel dust were in the range of 0.04–0.57 mg/m^3 in the 1980s (n = 1781), and 0.04–0.37 mg/m^3 in the 1990s (n = 1709).

Stridsklev *et al.* (2007) examined the relationship between the concentration of airborne nickel in the occupational environment of grinders (n = 9) grinding stainless steel in Norway and the concentration of nickel in their urine and blood. Grinders either worked in a well ventilated hall of a shipyard or in a small non-ventilated workshop. The sampling protocol was as follows: full-shift personal samples were collected in the breathing zone of grinders over the course of 1 work week; urine samples were collected three times daily for 1 week (first void in the morning, pre- and post-shift); and blood samples were drawn twice daily for 3 days in 1 week (pre- and post-shift). Blood and urine samples were also collected on the Monday morning after a 3-week vacation in the workshop. Grinders also completed a questionnaire to collect information on work history, use of personal protective equipment, and smoking habits. Mean levels of airborne nickel were 18.9 µg/m^3 (range, 1.8–88.6 µg/m^3) in the shipyard, and 249.8 µg/m^3 (range, 79.5–653.6 µg/m^3) in the workshop. Mean blood nickel levels for grinders were 0.87 µg/L (range, < 0.8–2.4 µg/L) in whole blood, and 1.0 µg/L (range, < 0.4–4.1 µg/L) in plasma. Mean urinary nickel levels for grinders were 3.79 µg/g creatinine (range, 0.68–10.6 µg/g creatinine), 3.39 µg/g creatinine (range, 0.25–11.1 µg/g creatinine), and 4.56 µg/g creatinine (range, < 0.53–11.5 µg/g creatinine), from the first void, pre- and post-shift samples, respectively. With the exception of stainless steel welders welding the MIG/MAG-method [Metal Inert Gas-Metal Active Gas], mean urinary nickel levels were higher in grinders than in welders. Mean urinary nickel levels in MIG/MAG welders were 5.9 µg/g creatinine (range, < 0.24–20.5 µg/g creatinine), 3.8 µg/g creatinine (range, 0.33–11.4 µg/g creatinine), and 4.6 µg/g creatinine (range, < 0.25–18.4 µg/g creatinine) from the first void, pre-, and post-shift samples, respectively.

Sivulka & Seilkop (2009) reconstructed historical exposures to nickel oxide and metallic nickel in the US nickel alloy industry from personal and area measurements collected at 45 plants since the 1940s (n = 6986 measurements). Of the measurements included in the database, 96% were personal breathing zone samples, and 4% were stationary area samples. The data provided evidence of a strongly decreasing gradient of airborne total nickel levels from the 1940s to the present.

1.5.3 Dietary exposure

Nickel has been measured in a variety of foodstuffs as “total nickel.” Average concentrations are in the range of 0.01–0.1 mg/kg, but can be as high as 8–12 mg/kg in certain foods (EVM, 2002; WHO, 2007). Factors influencing the concentration of nickel in food include the type of food (e.g. grains, vegetables, fruits versus seafood, mother’s milk versus cow’s milk), growing conditions (i.e. higher concentrations have been observed in food grown in areas of high environmental or soil contamination), and food preparation techniques (e.g. nickel content of cooking utensils, although the evidence for leaching from stainless steel cookware is somewhat mixed) (EVM, 2002; WHO, 2007).

The highest mean concentrations of nickel have been measured in beans, seeds, nuts and grains (e.g. cocoa beans, 9.8 µg/g; soyabeans, 5.2 µg/g; soya products, 5.1 µg/g; walnuts, 3.6 µg/g; peanuts, 2.8 µg/g; oats, 2.3 µg/g; buckwheat, 2.0 µg/g; and oatmeal, 1.8 µg/g). Although nickel concentrations vary by type of foodstuff, average levels are generally within the range of 0.01–0.1 µg/g. Reported ranges for some common food categories are: grains, vegetables and fruits, 0.02–2.7 µg/g; meats, 0.06–0.4 µg/g; seafood, 0.02–20 µg/g; and dairy, < 100 µg/L (EVM, 2002). This variability in nickel content makes it difficult to estimate the average daily dietary intake of nickel (EVM, 2002).

1.5.4 Biomarkers of exposure

Biomarker levels are influenced by the chemical and physical properties of the nickel compound studied, and by the time of sampling. It should be noted that the nickel compounds, the timing of collection of biological samples (normally at the end of a shift), and the analytical methods used differ from study to study, and elevated levels of nickel in biological fluids and tissue samples are mentioned only as indications of uptake of nickel, and may not correlate directly to exposure levels (IARC, 1990).

Atomic absorption spectrometry (AAS) and inductively coupled plasma atomic emission spectroscopy (ICP-AES) are the most common analytical methods used to determine “total nickel” concentrations in biological materials (such as blood, tissues, urine, and faeces). Nickel content can also be measured in other tissues, such as nails and hair, although specific procedures for dissolving the sample must be followed (ATSDR, 2005). The presence of calcium, sodium or potassium interferes with the quantification of nickel in biological samples, and specific techniques (e.g. isotope dilution) must be used to validate nickel measurements (ATSDR, 2005). Serum and urine samples are the most useful biomarkers of recent exposure, reflecting the amount of nickel absorbed in the previous 24–48 hours (NTP, 2000).

Minoia *et al.* (1990) used atomic absorption spectroscopy and neutron activation analysis to determine trace element concentrations of nickel in urine, blood, and serum collected from non-exposed healthy subjects (n = 1237; 635 males, 602 females) from the Lombardy region of northern Italy. The mean nickel level in urine samples (n = 878) was 0.9 µg/L (range, 0.1–3.9 µg/L); in blood samples (n = 36), 2.3 µg/L (range, 0.6–3.8 µg/L); and in serum samples (n = 385), 1.2 µg/L (range, 0.24–3.7 µg/L).

In a Norwegian-Russian population-based health study, human nickel exposure was investigated in the adult population living near a nickel refinery on both sides of the Norwegian-Russian border during 1994–95. Urine samples were collected from inhabitants, aged 18–69 years, of Nikel, Zapolyarny, and Sor-Varanger and also from individuals living more remotely from the Kola Peninsula nickel-producing centres (in the Russian cities of Apatity and Umba, and the Norwegian city of Tromso). A total of 2233 urine specimens were collected and analysed for nickel using electrothermal atomic absorption spectrometry. The highest urinary nickel concentrations were observed in residents of Nikel (median, 3.4 µg/L; mean, 4.9 µg/L; range, 0.3–61.9 µg/L), followed by Umba (median, 2.7 µg/L; mean, 4.0 µg/L; range, 1.0–17.0 µg/L), Zapolyarny (median, 2.0 µg/L; mean, 2.8 µg/L; range, 0.3–24.2 µg/L), Apatity (median, 1.9 µg/L; mean, 2.6 µg/L; range, 0.3–17.0 µg/L), Tromso (median, 1.2 µg/L; mean, 1.4 µg/L; range, 0.3–6.0 µg/L), and Sor-Varanger (median, 0.6 µg/L; mean, 0.9 µg/L; range, 0.3–11.0 g/L). The Russian participants all had a higher urinary nickel average than those from Norway, regardless of geographic location (Smith-Sivertsen *et al.*, 1998).

Ohashi *et al.* (2006) determined reference values for nickel in urine among women of the general population of 11 prefectures in Japan.

A total of approximately 13000 urine samples were collected in 2000–05 from 1000 adult women aged 20–81 years who had no occupational exposure to nickel. Nickel in urine was analysed by graphite furnace atomic absorption spectrometry. The observed geometric mean concentration for nickel was 2.1 μg/L (range, < 0.2–57 μg/L). After correction for creatinine, the geometric mean concentration was reported as 1.8 μg/L (maximum, 144 μg/L).

1.5.5 Other sources of exposure

Nickel, chromium, and cobalt are common causes of allergic contact dermatitis. In the early 1990s it was recommended that household and other consumer products should not contain more than 5 ppm of each of nickel, chromium, or cobalt, and that, for an even greater degree of protection, the ultimate target level should be 1 ppm. In a recent survey, selected consumer products had the following nickel levels (ppm): hand-wash powders, 0.9; heavy duty powders, 0.5; laundry tablets, 0.5; liquid/powder cleaners, 0.4; heavy duty liquids, 0.1; machine/hand-wash liquids, 0.1; hand-wash liquids, 0.1, fine wash liquids, 0.1; and dishwashing liquids, 0.1 (Basketter *et al.*, 2003).

Potential iatrogenic sources of exposure to nickel are dialysis treatment, leaching of nickel from nickel-containing alloys used as prostheses and implants, and contaminated intravenous medications (Sunderman, 1984).

2. Cancer in Humans

The previous *IARC Monograph* was based upon evidence of elevated risk of lung and nasal cancers observed among workers involved in a variety of nickel sulfide ore smelting and nickel refining processes that included high-temperature processing of nickel matte, nickel–copper matte, electrolytic refining, and Mond process refining. The exposures included metallic nickel, nickel oxides, nickel subsulfide, soluble nickel compounds, and nickel carbonyl. These cohort studies were conducted mainly in Canada, Norway, Finland, and in the United Kingdom (IARC, 1990; ICNCM, 1990).

2.1 Cohort studies and nested case–control studies

Since the previous *IARC Monograph*, several studies have extended follow-up to some of the previous cohorts, and have provided additional cohort and nested case–control analyses related mostly to lung cancer risk, and taking into account potential confounding factors as well as mixed exposures to water-soluble and -insoluble nickel compounds. Among the most common occupations with exposure to nickel compounds are stainless steel welders, who are also exposed to chromium (VI) compounds, and other compounds. Although there have been some cohort studies of stainless steel welders, these are not recorded in the present *Monograph* because it is difficult to ascribe any excess risks in these cohorts to nickel compounds specifically. Key results of some of these cohort studies can be found in Table 2.1 of the *Monograph* on chromium (VI) in this volume.

Also, since the previous *IARC Monograph*, experimental evidence has become available that nickel metal dust can become solubilized and bioavailable after inhalation. Consequently, separately classifying nickel and nickel compounds was viewed by the Working Group as not warranted. A similar distinction has not been made for other metals, e.g. beryllium and cadmium, in other *IARC Monographs*. Accordingly, this review did not exclude studies that focused on metallic nickel, unless they, for other reasons, were considered uninformative.

2.1.1 Cancer of the lung

Studies were carried out in nickel smelters and refineries in Canada, Norway (Kristiansand), Finland, and the United Kingdom (Clydach). Because the refining processes differed in the plants, the exposure profiles to various nickel compounds were different across the cohorts. Nonetheless, increased risks for lung cancer were found in cohorts from all of these facilities (see Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.1.pdf).

High risks for lung cancers were observed among calcining workers in Canada, who were heavily exposed to both sulfidic and oxidic nickel (nickel sulfides and oxides). A high lung cancer rate was also seen among nickel plant cleaners in Clydach who were heavily exposed to these insoluble compounds, with little or no exposure to soluble nickel. The separate effects of oxides and sulfides could not be estimated, however, as high exposure was always either to both, or to oxides together with soluble nickel. Workers in Clydach calcining furnaces and nickel plant cleaners, exposed to high levels of metallic nickel, had high lung cancer risks (see Table 2.1 online). A substantial excess risk for lung cancer among hydrometallurgy workers in Norway was mainly attributed to their exposure to water-soluble nickel. Their estimated exposures to other types of nickel (metallic, sulfidic, and oxidic) were as much as an order of magnitude lower than those in several other areas of the refinery, including some where cancer risks were similar to those observed in hydrometallurgy. High risks for lung cancer were also observed among electrolysis workers at Kristiansand (Norway). These workers were exposed to high estimated levels of soluble nickel and to lower levels of other forms of nickel. Nickel sulfate and nickel chloride (after 1953) were the only or predominant soluble nickel species present in these areas.

An update of the Kristiansand cohort by Andersen *et al.* (1996) demonstrated a dose–response relationship between cumulative exposure to water-soluble nickel compounds and lung cancer ($P < 0.001$) when adjustment was made for age, smoking, and nickel oxide. The risk was increased 3-fold in the highest soluble nickel dose group. A lesser, but positive, effect was seen between cumulative exposure to nickel oxide and risk of lung cancer, also with adjustment for age, cigarette smoking, and exposure to water-soluble nickel (P for trend = 0.05, see Table 2.2).

Subsequent to the Andersen *et al.* (1996) study, an industrial hygiene study re-evaluated exposure among the Norwegian refinery workers based on new information related to nickel species and exposure levels (Grimsrud *et al.*, 2000). Grimsrud *et al.* (2003) updated the lung cancer incidence among the Norwegian nickel refinery workers (see Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.3.pdf). The strongest gradient for cumulative exposure and lung cancer was found in relation to water-soluble nickel adjusted for cigarette-smoking habits, which was known for 4728 (89%) of the cohort members. Regarding species of water-soluble nickel compounds, the risk from potential exposure to nickel chloride was similar to that for nickel sulfate. The nickel electrolysis process (using nickel sulfate) changed to a nickel-chloride-based process in 1953, and workers hired in 1953 or later had a similar lung cancer risk (standardized incidence ratio [SIR], 4.4; 95%CI: 1.8–9.1) as for those employed in the same area before 1953 when the nickel sulfate was used (SIR, 5.5; 95%CI: 3.0–9.2). Analyses by year of first employment indicated that those initially employed after 1978 continued to demonstrate a significantly elevated risk of lung cancer (SIR, 3.7; 95%CI: 1.2–8.7), suggesting continued exposure to nickel compounds.

Grimsrud *et al.* (2002) conducted a case–control study of lung cancer nested within the

Table 2.2 Relative risks of lung cancer by cumulative exposure to soluble nickel and nickel oxide, considering the two variables simultaneously by multivariate Poisson regression analysis[a]

Variable	Mean exposure (mg/m^3)	Cases	Relative risk	95%CI	Test for linear trend
Soluble nickel					*P* < 0.001
< 1	0.1	86	1.0	Referent	
1–4	2.3	36	1.2	0.8–1.9	
5–14	8.8	23	1.6	1.0–2.8	
≥ 15	28.9	55	3.1	2.1–4.8	
Nickel oxide					*P* = 0.05
< 1	0.4	53	1.0	Referent	
1–4	2.5	49	1.0	0.6–1.5	
5–14	8.3	53	1.6	1.0–2.5	
≥ 15	44.3	45	1.5	1.0–2.2	

[a] Workers with unknown smoking habits were excluded (three cases of lung cancer).
Adjusted for smoking habits and age.
From Andersen *et al.* (1996)

cohort of Norwegian nickel refinery workers (see Table 2.3 online). Exposure groups were determined based on quintiles of the exposure variables in the controls. Analyses by cumulative exposure adjusted for cigarette smoking indicated that odds ratios for lung cancer in the highest cumulative exposure category of water-soluble nickel, sulfidic nickel, metallic nickel, and oxidic nickel were 3.8 (95%CI: 1.6–9.0), 2.8 (95%CI: 1.1–6.7), 2.4 (95%CI: 1.1–5.3), and 2.2 (95%CI: 0.9–5.4), respectively. The trend for cumulative exposure and lung cancer was significant for water-soluble nickel compounds only (*P* = 0.002). There was, however, a high degree of correlation with exposure to nickel and nickel compounds as a whole, making evaluation of the independent effect of individual compounds difficult. Nonetheless, when data were further adjusted for exposure to water-soluble compounds, there were no significant trends in the odds ratios by cumulative exposure to sulfidic, oxidic, or metallic nickel. The odds ratios related to the highest cumulative exposure group for each of these compounds were 1.2 (95%CI: 0.5–3.3), 0.9 (95%CI: 0.4–2.5), and 0.9 (95%CI: 0.3–2.4), respectively (see Table 2.4). In further analyses, with adjustment for cigarette smoking, arsenic, asbestos, sulfuric acid mist, cobalt and occupational carcinogenic exposures outside the refinery, the strong association between lung cancer and water-soluble nickel remained (Grimsrud *et al.*, 2005).

Anttila *et al.* (1998) updated an earlier cohort study of Finnish nickel refinery and copper/nickel smelter workers (Karjalainen *et al.*, 1992). Among refinery workers employed after 1945, who were exposed primarily to nickel sulfate, an excess of lung cancer was observed in the overall cohort (SIR, 2.61; 95%CI: 0.96–5.67), and the lung cancer risk increased with > 20 years of latency (SIR, 3.38; 95%CI: 1.24–7.36, based on six cases). Among smelter workers, lung cancer was also elevated in the overall cohort (SIR, 1.39; 95%CI: 0.78–2.28), and, similarly, a significant increase in lung cancer risk with > 20 years of latency was observed (SIR, 2.00; 95%CI: 1.07–3.42).

There have been three subsequent reports that provide additional information on refinery workers in Wales (the United Kingdom) exposed to nickel carbonyl and other nickel compounds.

Easton *et al.* (1992) carried out an updated analysis of Welsh nickel refinery workers to determine which nickel compounds were responsible for lung cancer among the 2524 workers employed

Table 2.4 Adjusted[a] odds ratios for lung cancer by exposure to sulfidic, oxidic or metallic nickel in a nested case–control study of Norwegian nickel refinery workers observed during 1952–95

Cumulative exposure to nickel[b]	Odds ratio	95% CI
Sulfidic nickel		
Unexposed	1.0	
Low	1.5	0.6–3.9
Low-medium	2.2	0.9–5.5
Medium	1.8	0.7–4.5
Medium-high	1.3	0.5–3.3
High	1.2	0.5–3.3
Likehood ratio test: $P = 0.344$		
Oxidic nickel		
Unexposed	1.0	
Low	1.5	0.6–3.8
Low-medium	1.8	0.7–4.5
Medium	1.4	0.6–3.7
Medium-high	1.5	0.6–3.7
High	0.9	0.4–2.5
Likehood ratio test: $P = 0.406$		
Metallic nickel		
Unexposed	1.0	
Low	1.2	0.5–2.9
Low-medium	1.0	0.5–2.4
Medium	1.0	0.4–2.3
Medium-high	1.0	0.4–2.4
High	0.9	0.3–2.4
Likehood ratio test: $P = 0.972$		

[a] Data were adjusted for smoking habits in five categories (never smoker, former smoker, or current smoker of 1–10, 11–20, or > 20 g/day), and for exposure to water-soluble nickel as a continuous variable with natural log-transformed cumulative exposure values (ln[(cumulative exposure) + 1]).
[b] Categories were generated according to quartiles among exposed control. In each of the three analyses, data were unadjusted for the other two insoluble forms of nickel.
From Grimsrud *et al.* (2002)

for > 5 years before the end of 1969, and followed during 1931–85. The model was based on exposures occurring before 1935, and was adjusted for age at first exposure, duration of exposure, and time since first exposure. For lung cancer, the best fitting model suggested risks for soluble and metallic nickel exposures, and much less (if any) risk for nickel oxide or sulfides. Sorahan & Williams (2005) followed during 1958–2000 a group of 812 workers from the cohort of Welsh nickel refinery workers who were hired between 1953–92, and who had achieved > 5 years of employment. The overall lung cancer SMR was 1.39 (95%CI: 0.92–2.01). For those with > 20 years since the start of employment, lung cancer risk was significantly elevated [SMR, 1.65; 95%CI: 1.07–2.41], indicating an elevated risk of lung cancer among those hired since 1953.

Grimsrud & Peto (2006) combined data from the most recent updates of Welsh nickel refinery workers to assess lung cancer mortality risk by period of initial employment. For those first employed since 1930, an elevated risk was observed for lung cancer (SMR, 1.33; 95%CI: 1.03–1.72). [The Working Group noted that

exposures were dramatically reduced during the 1920s.]

Egedahl *et al.* (2001) updated the mortality data among employees at a hydrometallurgical nickel refinery and fertilizer complex in Fort Saskatchewan, Canada, who had worked for 12 continuous months during 1954–78. Among the 718 men exposed to nickel, the lung cancer SMR was 0.67 (95%CI: 0.24–1.46, based on six deaths). Significant decreases were observed for the 'all causes of death' category (SMR, 0.57; 95%CI: 0.43–0.74), and for the 'all cancer deaths' category (SMR, 0.47; 95%CI: 0.25–0.81). [The Working Group considered the study uninformative for the evaluation of cancer risks due to a substantial healthy worker effect which may have masked excess mortality that was associated with nickel exposure.]

Goldberg *et al.* (1994) conducted a 10-year incidence study and a nested case–control study of a cohort of nickel mining (silicate-oxide ores) and refinery workers in New Caledonia, South Pacific. They observed a significant decrease in the incidence of lung cancer, and this was also observed for other respiratory cancers The results of the case–control study did not show elevated risks for respiratory cancers in relation to low levels of exposure to soluble nickel, nickel sulfide, or metallic nickel. For all three nickel exposures separately, the odds ratios were 0.7.

[The Working Group noted that in most of these studies of lung cancer risk in smelters and refineries, there was exposure to metallic nickel together with exposure to the other forms of nickel (Sivulka, 2005). Only one of these studies involved an attempt to evaluate separately the effect of metallic nickel (Grimsrud *et al.*, 2002).]

Several additional studies of workers with potential exposure to metallic nickel were reviewed by the Working Group. Arena *et al.* (1998) evaluated mortality among workers exposed to "high nickel alloys" in the USA. A recent industrial hygiene analysis indicated that oxidic nickel comprised 85% of the total nickel exposure of these workers, with the rest being mostly metallic nickel (Sivulka & Seilkop, 2009). Compared to US national rates, lung cancer was significantly elevated among white men (SMR, 1.13; 95%CI: 1.05–1.21), among non-white men the SMR was 1.08 (95%CI: 0.85–1.34), and in women 1.33 (95%CI: 0.98–1.78). [The Working Group noted that the lung cancer SMR for the entire cohort combined was 1.13 (95%CI: 1.06–1.21) based on 955 observed deaths.] The authors also calculated SMRs based on local (SMSA) rates for the separate population subgroups. When calculated for the total cohort, the resulting SMR was [1.01; 95%CI: 0.95–1.08]. [The Working Group noted that it is difficult to interpret the use of local rates when the study population was derived from 13 separate areas located throughout the USA, but the use of rates from urban areas could have overestimated the expected number of deaths from lung cancer. The Working Group noted that the overall SMR for lung cancer in this study compared with the national population was statistically significant, and provides some evidence of an association between exposures in these plants and lung cancer. It appears that the primary exposure was to nickel oxide and thus, the study cannot be used to evaluate the specific carcinogenicity of metallic nickel. Analysis of lung cancer by duration of employment did not indicate a dose–response. The Working Group noted that duration of employment is a poor measure of exposure when exposures are known to have declined over time.]

There have also been a series of studies conducted in the French stainless steel industry that involved co-exposure to several known and potential human lung carcinogens, and the most detailed exposure assessment considered nickel and chromium combined (Moulin *et al.* 1990, 1993a, b, 1995, 2000).]

The only cohort of workers exposed to metallic nickel in the absence of other nickel compounds (Oak Ridge cohort) included only 814 workers, and provided little statistical power to evaluate

lung cancer risk (Godbold & Tompkins, 1979; Cragle *et al.*, 1984).

Sorahan (2004) updated the mortality rate among employees manufacturing nickel alloys at the plant in Hereford, the United Kingdom. The study showed a significant decrease for 'all causes of death' (SMR, 0.79), for 'all cancer deaths' (SMR, 0.81), and a non-significant decrease for lung cancer (SMR, 0.87; 95%CI: 0.67–1.11).

Pang *et al.* (1996) evaluated cancer risks among 284 men who were employed for at least 3 months during 1945–75 in a nickel-plating department, and followed through 1993. For lung cancer, the overall SMR was 1.08 (95%CI: 0.54–1.94). For those with > 20 years latency, eight lung cancer deaths were observed versus 6.31 expected [SMR, 1.27; 95%CI: 0.55–2.50].

Several other studies reviewed by Sivulka (2005) had mixed exposure to metallic nickel and other nickel compounds, and provide no evidence on the carcinogenicity of metallic nickel alone. Furthermore, many of the studies cited in the review involved mixed exposures in stainless steel welding and grinding, and manufacturing nickel alloys (Cox *et al.*, 1981; Enterline & Marsh, 1982; references from Tables 5 and 6 of Sivulka, 2005), and therefore were not considered relevant for evaluating the carcinogenicity of nickel and/or nickel compounds.

2.1.2 Cancer of the nasal cavity

Increased risks for nasal cancers were found to be associated with exposures during high-temperature oxidation of nickel matte and nickel-copper matte (roasting, sintering, calcining) in cohort studies in Canada, Norway (Kristiansand), and the United Kingdom (Clydach), with exposures in electrolytic refining in a study in Norway, and with exposures during leaching of nickel-copper oxides in acidic solution (copper plant), and extraction of nickel salts from concentrated solution (hydrometallurgy) in the United Kingdom (see Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.5.pdf).

In the Norwegian study, Andersen *et al.* (1996) demonstrated a dose–response relationship between both cumulative exposure to water-soluble nickel and nickel oxide compounds and the risk of nasal cancer. The SIR (compared to the general population) was the highest in the group of workers with the highest cumulative exposure to soluble nickel compounds combined with insoluble nickel compounds (SIR, 81.7; 95%CI: 45–135; based on 15 cases). For workers with the highest cumulative exposure to nickel oxide, the SIR was 36.6 (95%CI: 19.5–62.5; based on 13 cases) (see Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.6.pdf).

An update of nasal cancer in Finnish refinery workers after 20 years since the first exposure to nickel reported an SIR of 67.1 (95%CI: 12–242.0; based on two cases) (Anttila *et al.*, 1998). An additional nasal cancer was observed 2 years after the follow-up period ended, and a fourth potential nasal cancer (classified as a nasopharyngeal cancer, 0.04 expected) was reported during the follow-up period. No nasal cancers were observed among the smelter workers who were exposed primarily to nickel matte, nickel subsulfide, nickel sulfides, and other metals.

Easton *et al.* (1992) attempted to identify the nickel compounds responsible for nasal cancer among 2524 Welsh nickel refinery workers employed for > 5 years before the end of 1969, and followed during 1931–85. As shown in Table 2.7, the risk for nasal cancer was in the range of 73–376 times the expected for those first employed before 1930, based on 67 nasal cancer deaths. A statistical model that fitted to the data on men whose exposures occurred before 1935, and that adjusted for age at first exposure, duration of exposure, and time since first exposure indicated that the soluble nickel effect on nasal cancer risk is the only one significant.

Table 2.7 Observed and expected deaths from nasal sinus cancer (1931–85) by year of first employment

Year first employed	Observed deaths	Expected deaths	SMR	95% CI
< 1920	55	0.15	376	276–477
1920–29	12	0.17	73	36–123
1930–39	1	0.07	14	0.4–80
1940–49	0	0.06	–	–
> 1950	0	0.06	–	–
Total	68	0.45	151	117–192

From Easton *et al.* (1992)

Grimsrud & Peto (2006) combined data from the most recent updates of Welsh nickel refinery workers to assess nasal cancer mortality risk by period of initial employment. For those first employed since 1930, an elevated risk was observed for nasal cancer (SMR, 8.70; 95%CI: 1.05–31.41, based on two observed deaths).

In one study of Swedish Ni–Cd battery workers, three nasal cancer cases versus 0.36 expected were observed (SIR, 8.32; 95%CI: 1.72–24.30) (Järup *et al.*, 1998). Two of these cases occurred among workers exposed to greater than 2 mg/m^3 nickel (SIR, 10.8; 95%CI: 1.31–39.0).

2.1.3 Other cancer sites

Other than for lung cancer and nasal sinus cancer, there is currently no consistency in the epidemiological data to suggest that nickel compounds cause cancer at other sites.

The results of several studies of workers exposed to nickel compounds showed a statistically elevated risk of a site-specific cancer in addition to lung and nasal cancer. A study of sinter plant workers in Canada showed a significantly elevated risk of cancer of the buccal cavity and pharynx (IARC, 1990). In a study in the Norwegian nickel-refining industry, a significant excess of laryngeal cancer was observed among roasting and smelter workers (Magnus *et al.*, 1982).

Stomach cancer was significantly elevated among men employed in a nickel- and chromium-plating factory in the United Kingdom (Burges, 1980). A study of men employed in a nickel-plating department (Pang *et al.*, 1996) showed a significant elevation in stomach cancer. Another study (Anttila *et al.*, 1998) demonstrated a significant excess of stomach cancer among nickel refinery workers.

A study of workers producing alloys with a high nickel content (Arena *et al.*, 1998) demonstrated a significant excess of colon cancer among ‘non-white males’ (relative risk, 1.92; 95%CI: 1.28–2.76), and a 2-fold risk of kidney cancer among white males employed in ‘melting.’ However, the excess risk was not associated with length of employment or time since first employment. [The Working Group noted that specific data was not provided in the article.]

A meta-analysis (Ojajärvi *et al.*, 2000) reported a significantly elevated risk for pancreatic cancer that upon further evaluation actually indicated no elevation in risk (Seilkop, 2002).

A population-based case–control study (Horn-Ross *et al.*, 1997) based on self-reported occupational exposure, showed a dose–response relationship between cumulative exposure to nickel compounds/alloys and salivary gland cancer. [The Working Group noted that the author corrected the direction of signs in Table 2 of her report in a subsequent erratum.]

2.2 Synthesis

The Working Group evaluated a large body of evidence and concluded that there is an elevated risk of lung and nasal sinus cancer among nickel refinery workers (IARC, 1990; Andersen *et al.*, 1996; Anttila *et al.*, 1998; Grimsrud & Peto, 2006), and an elevation in lung cancer risk among nickel smelter workers (IARC, 1990; Anttila *et al.*, 1998).

Epidemiological studies have provided evidence for lung cancer related to specific nickel compounds or classes of compounds (based, for example, on water solubility). Evidence for elevated risk of lung cancer in humans was demonstrated specifically for nickel chloride (Grimsrud *et al.*, 2003), nickel sulfate, water-soluble nickel compounds in general (Andersen *et al.*, 1996; Grimsrud *et al.*, 2002, 2003; Grimsrud *et al.*, 2005), insoluble nickel compounds, nickel oxides (Andersen *et al.*, 1996; Anttila *et al.*, 1998; Grimsrud *et al.*, 2003), nickel sulfides (Grimsrud *et al.*, 2002), and mostly insoluble nickel compounds (Andersen *et al.*, 1996).

A study that modelled risks of various nickel compounds and lung cancer risk identified both water-soluble nickel and metallic nickel as contributing to risk (Easton *et al.*, 1992). The largest study addressing worker exposure to metallic nickel (in combination with nickel oxide) showed a small but significant elevation in lung cancer risk (Arena *et al.*, 1998).

Other studies specifically addressing nickel metal exposures were uninformative and did not allow any judgment as to whether such exposures should be considered different with regard to cancer risk. It was not possible to entirely separate various nickel compounds in dose–response analyses for specific nickel compounds. In one analysis, an additional adjustment for water-soluble nickel compounds on risk of lung cancer indicated little association with cumulative exposure to sulfidic, oxidic or metallic nickel. One study of Ni–Cd battery workers exposed to nickel hydroxide and cadmium oxide demonstrated a significant risk of cancer of the nose and nasal sinuses.

On the basis of the Norwegian studies of refinery workers, the evidence is strongest for water-soluble nickel compounds and risk for lung cancer. The confidence of the Working Group in the above findings was reinforced by the availability of information on cigarette smoking for 89% of the Norwegian cohort, and the adjustments made for potential confounding exposures.

3. Cancer in Experimental Animals

Nickel and nickel compounds have been tested for carcinogenicity by intramuscular injection to rats, mice, and rabbits; by repository injections at multiple sites in hamsters, rabbits and mice; by intraperitoneal administration to rats and mice; and by intratracheal instillation, intrapleural, intrarenal, intraocular, inhalation, and subcutaneous exposure to rats.

Particularly relevant studies reviewed in the previous *IARC Monograph* (IARC, 1990) were reconsidered in this evaluation, and summarized in the text.

3.1 Oral administration

3.1.1 Nickel sulfide

In a 2-year multiple dose study, oral nickel sulfate hexahydrate given to male and female rats did not result in carcinogenesis (Heim *et al.*, 2007).

3.1.2 Nickel chloride

Nickel chloride was tested for carcinogenicity by oral administration in female hairless mice (CRL: SK1-hrBR). Mice were exposed to ultraviolet radiation (UVR) alone, nickel chloride alone (given in the drinking-water) and UVR + various concentrations of nickel chloride. Nickel

Table 3.1 Studies of cancer in experimental animals exposed to nickel compounds (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) 104 wk Heim *et al.* (2007)	Nickel sulfate hexahydrate 0, 10, 30, 50 mg/kg/d (gavage),[a] 60/group/sex	Keratoacanthoma (tail): M–low dose 15% (numbers not provided)	$P < 0.001$	Age at start, 6 wk 99.9% pure Exposure-related decreased bw in males and females (2 highest dose groups) Exposure-related increased mortality ($P_{trend} < 0.008$) in high dose females but not males
Mouse, CRL: Sk1-hrBR (F) 224 d Uddin *et al.* (2007)	Nickel chloride in drinking-water at 3 wk of age 3 wk later UV treatment (1.0 kJ/m²) 3 d/wk for 26 wk Groups, number of animals Group 1: Controls, 5 Group 2: UV only, 10 Group 3: 500 ppm, 10 Group 4: UV + 20 ppm, 10 Group 5: UV + 100 ppm, 10 Group 6: UV + 500 ppm, 10 5–10/group	Skin (tumours): Number of tumours/mice at 29 wk Group 1: 0 Group 2: 1.7 ± 0.4 Group 3: 0 Group 4: 2.8 ± 0.9 Group 5: 5.6 ± 0.7 Group 6: 4.2 ± 1.0	Group 5 vs Group2 $P < 0.05$ Group 6 vs Group 2 $P < 0.05$	Age at start, 3 wk Nickel had no effect on growth of the mice Nickel levels in skin increased with dose

[a] vehicle not stated
d, day or days; F, female; M, male; UVR, ultraviolet radiation; vs, versus; wk, week or weeks

chloride alone did not cause skin tumours by itself, but when combined with UVR, it increased the UVR-induced skin tumour incidence (Uddin *et al.*, 2007).

See Table 3.1.

3.2 Inhalation exposure

3.2.1 Nickel sulfate hexahydrate

Nickel sulfate hexahydrate was not shown to be carcinogenic in male or female rats or male or female mice when given by inhalation in a 2-year bioassay study (Dunnick *et al.*, 1995; NTP, 1996a). Analysis of lung burden showed that nickel was cleared from the lungs (Dunnick *et al.*, 1995).

3.2.2 Nickel subsulfide

Nickel subsulfide induced lung tumours in rats exposed by inhalation (Ottolenghi *et al.*, 1975).

Inhalation of nickel subsulfide increased the incidence of aveolar/bronchiolar adenomas and carcinomas in male F344 rats, and increased combined lung tumours in females (Dunnick *et al.*, 1995; NTP, 1996b). Nickel subsulfide also increased the incidence of adrenal pheochromocytomas (benign or malignant) in male and female rats, malignant pheochromocytomas were increased in male rats. Significant dose-related trends were observed for both lung and adrenal tumours in both sexes.

3.2.3 Nickel oxide

The carcinogenicity of nickel oxide was investigated in 2-year inhalation studies in F344 male and female rats, and B6C3F$_1$ male and female mice. Nickel oxide induced tumours of the lung (aveolar bronchiolar adenomas or carcinomas), and adrenal medulla (malignant and benign pheochromocytoma) in both sexes of rats. Nickel oxide also increased the incidence of lung tumours in low-dose females but not in male mice (NTP, 1996c).

3.2.4 Metallic nickel

Inhaled metallic nickel increased the incidence of adrenal pheochromocytomas (benign, malignant, and benign and malignant combined) in male rats and adrenal cortex tumours in female rats (Oller *et al.*, 2008). Dose-related responses were observed for both types of adrenal tumours. No significant increases in lung tumours occurred. Elevated blood levels of nickel indicated that metallic nickel was bioavailable systematically after inhalation (Oller *et al.*, 2008).

3.2.5 Other forms of nickel

Nickel carbonyl induced lung carcinomas after inhalation exposure (Sunderman *et al.*, 1957, 1959).

See Table 3.2.

3.3 Parenteral administration

3.3.1 Nickel subsulfide

(a) Mouse

Nickel subsulfide induced local sarcomas after repository injections at multiple sites in numerous studies in mice (IARC, 1990).

No increase in lung tumour incidence was observed in male strain A/J mice, 20 or 45 weeks after exposure to various treatment regimens of nickel subsulfide (McNeill *et al.*, 1990). In another study, nickel subsulfide induced injection-site tumours in all three strains of mice, with the order of susceptibility to tumour formation being C3H, B6C3F$_1$, and C57BL6 (Rodriguez *et al.*, 1996). Waalkes *et al.* (2004, 2005) studied the carcinogenic response to nickel subsulfide in MT-transgenic and MT-null mice. Intramuscular administration of nickel subsulfide increased the incidence of injections-site tumours (primarily fibrosarcoma) in MT-transgenic and concordant wild-type mice, and lung tumours in MT-transgenic mice (Waalkes *et al.*, 2004). In MT-null mice and concordant wild-type mice, intramuscular injection of nickel sulfide induced fibrosarcomas as well (Waalkes *et al.*, 2005). MT-expression, either overexpression (MT-transgenic mice) or no expression (MT-null), did not significantly affect the carcinogenic response to nickel.

(b) Rat

Nickel subsulfide induced lung tumours in rats exposed by intratracheal instillation (Pott *et al.*, 1987). Intrarenal injection resulted in dose-related increases in renal cell tumours, and intraocular injection resulted in eye tumours in rats (Jasmin & Riopelle, 1976; Sunderman *et al.*, 1979; Albert *et al.*, 1980; Sunderman, 1983). Implantation of nickel subsulfide pellets into rat heterotropic tracheal transplant caused carcinomas and sarcomas (Yarita & Nettesheim, 1978). Local tumours were also observed in rats tested by intramuscular and intrarenal injection with nickel disulfide or nickel monosulfide (crystalline but not amorphous form), and in rats tested by intramuscular injection with nickel ferrosulfide matte (Sunderman, 1984; Sunderman *et al.*, 1984).

When administered by intrarenal injection to F344 male rats, nickel subsulfide induced renal sarcomas (Kasprzak *et al.*, 1994), which showed metastases to the lung, liver, and spleen. Injection site tumours (rhabdomyosarcoma,

Table 3.2 Studies of cancer in experimental animals exposed to nickel compounds or nickel powder (inhalation exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel sulfate hexahydrate				
Rat, F344 (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996a)	0, 0.125, 0.25, 0.5 mg/m^3 (equivalent to 0, 0.03, 0.06, 0.11 mg nickel/m^3) for 6 h/d, 5 d/wk 63–65/group/sex	Lung (aveolar/bronchiolar adenomas or carcinomas or squamous cell carcinomas): M–2[a]/54 (12.5%), 0/53 (0.0%), 1/53 (4.0%), 3/53 (11.8%) F[b]–0/52, 0/53, 0/53, 1/54 (2%) Adrenal medulla (pheochromocytomas, benign or malignant[c]): M–16/54 (61.2%), 19/53 (66%), 13/53 (50.7%), 12/53 (47.4%) F–/52 (6.6%), 4/52 (19.7%), 3/52 (9.2%), 3/54 (10.3%)		Age at start, 6 wk 22.3% Nickel No treatment-related effects on survival. Mean bw of high-dose females were slightly lower than controls. Nickel lung burden values increased with increasing exposure (at 15 mo, 0.15–1.7 µg Ni/g lung)
Mouse, B6C3F$_1$ (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996a)	0, 0.25, 0.5, 1.0 mg/m^3 (equivalent to 0, 0.06, 0.11, 0.22 mg nickel/ m^3) 6 h/d, 5 d/wk 63–65/group/sex	Lung (aveolar/bronchiolar adenomas or carcinomas): M–13/61 (43.6%), 18/61 (64.5%), 7/62 (21.2%), 8/61 (26.2%) F–7/61 (19.3%), 6/60 (13.9%), 10/60 (21.1%), 2/60 (4.3%)		Age at start, 6 wk 22.3% Nickel No treatment-related effects on survival. Bw of high-dose males and all exposed female groups were decreased Nickel lung burden (µg Ni/g lung) below limit of detection at 7 and 15 mo interim evaluations
Nickel subsulfide				
Rat, F344 (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996b)	0, 0.15, 1 mg/m^3 (equivalent to 0, 0.11, 0.73 mg nickel/m^3) 6 h/d, 5 d/wk 63/group/sex	Lung (aveolar/bronchiolar adenomas or carcinomas or squamous cell carcinomas): M–0/53 (0), 6/53 (19.7%), 11/53 (48.1%) F–2/53 (8.0%), [a]6/53 (20.0%), 9/53 (27.2%) Adrenal medulla (pheochromocytomas, benign or malignant):	M: mid dose $P < 0.05$, high dose $P \leq 0.01$, $P_{trend} < 0.01$ F: mid dose $P \leq 0.05$ vs historical control, high dose $P < 0.05$, $P_{trend} < 0.05$	Age at start, 6 wk 73.3% Nickel No treatment-related effects on survival. Bw in high-dose groups Nickel lung burden increased with increasing exposure but reached steady-state by 15 mo (4–7 µg Ni/g lung). Lung carcinomas also were significantly increased in high-dose males

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996b) (contd.)		M–14/53 (55.4%), 30/53 (84.6%), 42/53 (100.0%) F–3/53 (10.4%), 7/53 (24.4%), 36/53 (85.5%)	M: mid dose $P < 0.01$, high dose < 0.001, P_{trend} < 0.001 F: high dose, $P < 0.001$ $P_{trend} < 0.001$	
Mouse, $B6C3F_1$ (M, F) 104 wk Dunnick *et al.* (1995), NTP 1996b	0, 0.6, 1.2 mg/m³ (equivalent to 0, 0.44, 0.9 mg nickel/m³) 6 h/d, 5 d/wk 63/group	Lung (aveolar/bronchiolar adenomas or carcinomas): M–13/61 (40.7%), 5/59 (18.5%), 6/58 (21.4%) F–9/58 (24.1%), 2/59 (4.8%), 3/60 (7.9%)	$P = 0.038N^h$ mid dose vs control $P = 0.028N^h$ mid dose vs control $P = 0.050N^h$ high dose vs control	Age at start, 6 wk 73.3% Nickel No treatment-related effects on survival. Mean bw lower in exposed groups than control group. Nickel lung burden increased with exposure concentration and with time (at 15 mo, 12–26 µg Ni/g lung)

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) 78–80 wk + held 30 wk Ottolenghi *et al.* (1975)	Nickel subsulfide with or without 1 mo pre-exposure to the airborne system (clean air or nickel sulfide dust 0.97 ± 0.18 mg/m^3 for 5 d/wk), followed by injection of hexachlorotetrafluorobutane to half the animals, thereafter the inhalation exposure was continued for all animals 16 exposure groups (8 groups/sex) <u>Pre-exposure</u> Inj. Controls: 29 (M), 28 (F) Inj. NiS: 29 (M), 28 (F) No Inj. Controls: 28 (M), 30 (F) No Inj. NiS: 22 (M), 26 (F) <u>No Pre-exposure</u> Inj. Controls: 32 (M), 32 (F) Inj. NiS: 24 (M), 32 (F) No Inj. Controls: 31 (M), 31 (F) No Inj. NiS: 32 (M), 26 (F)	Lung (adenomas, adenocarcinomas, squamous cell carcinomas, fibrosarcomas): NiS–17 (M), 12 (F) Controls–1 (M), 1 (F) Adrenal gland (hyperplasias and pheochromocytomas): NiS–12% Controls–1.1%	 M, F: $P < 0.01$ $P < 0.01$	Pre-exposure: animals assigned airborne system for 1 mo No pre-exposure: animals housed in normal conditions for 1 mo Inj. = intravenous injection with pulmonary infraction agent Treatment-related decreased survival and decreased bw in males and females starting at 26 wk Inflammatory response – pneumonitis, bronchitis and emphysema Hyperplasias and squamous metaplasic changes in bronchial and bronchiolo-alveolar regions Infraction had no effect on carcinogenicity

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel oxide				
Rat, F344 (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996c)	0, 0.62, 1.25, 2.5 mg/m^3 (equivalent to 0, 0.5, 1.0, 2.0 mg nickel/ m^3) 6 h/d, 5 d/wk 65/group/sex	Lung (aveolar/bronchiolar adenomas or carcinomas, or squamous cell carcinomas): M– 1[a]/54 (7.1%), 1/53 (2.6%), 6/53 (27.7%), 4/52 (23.7%) F–1/53 (4.8%), 0/53[d] (0.0%), 6/53 (24.7%), 5/54 (19%) Adrenal medulla (pheochromocytomas, benign or malignant): M–27/54 (81.8%), 24/53 (69.3%), 27/53 (83.6%), 35/542 (97.0%) F[e]–4/51 (15.1%), 7/52 (21.1%), 6/53 (22.0%), 18/54 (56.5%)	M, F: mid dose & high dose, $P \leq 0.05$ vs high dose M: high dose, $P = 0.027$, $P_{trend} = 0.008$ F: high dose, $P = 0.01$, $P_{trend} < 0.001$	Age at start, 6 wk 76.6% Nickel No treatment-related effects on survival or bw Nickel lung burden increased with exposure and with time (at 15 mo, 262–1116 µg Ni/lung) If the squamous cell carcinomas (lung tumours) are not included, then the mid dose and high dose are significant vs the current controls Significantly increased incidence of malignant pheochromocytomas in high-dose males
Mouse, B6C3F$_1$ (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996b)	0, 1.25, 2.5, 5.0 mg/m^3 (equivalent to 0, 1.0, 2.0, 3.9 mg nickel/m^3) 6 h/d, 5 d/wk ≈80/group/sex	Lung (aveolar/bronchiolar adenomas or carcinomas): M–9/57 (36.3%), 14/67 (41.4%), 15/66 (43.6%), 14/69 (39.7%) F–6/64 (13.8%), 15/66 (30.8%), 12/63 (25.7%), 8/64 (17.4%)	F: low dose, $P \leq 0.01$	Age at start, 6 wk; 76.6% Nickel No treatment-related effects on survival or bw Nickel lung burden increased with exposure and with time (at 15 mo, 331–2258 µg Ni/lung)

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel metal powder				
Rat, Wistar Crl:Wi (G1XBRl/ Han) (M, F) 12–30 mo Oller *et al.* (2008)	0, 0.1, 0.4, 1 mg/m^3 for 6 h/d, 5 d/wk, exposure time, additional hold time– Group 1: 0, 24 mo, 6 mo Group 2: 0.1, 24 mo, 6 mo Group 3, F: 0.4, 19 mo, 11 mo Group 3, M: 0.4, 24 mo, 6 mo Group 4, F: 1.0, ~14 mo, 0 mo Group 4, M: 1.0, ~12 mo, 0 mo 50/group	Groups 1, 2, 3 Adrenal gland (pheochromocytomas, benign or malignant): M–0/50, 5/50 (10%), 21/50 (42%) F–0/50, 5/49 (10%), 3/53 (6%) Adrenal cortex (adenomas or carcinomas): M–1/50 (2%), 3/50 (6%), 2/50 (4%) F–2/50 (4%), 2/49 (4%), 7/54 (13%)	M: 0.4 mg/m^3 Significant increase for benign, malignant, benign combined, significant dose-related response[f] F: 0.4 mg/m^3 Significant increase for combined (adenoma and carcinoma) and significant dose-related response[f]	Age at start, 6 wk 99.9% pure Exposure-related mortality was observed in the high-dose group (Group 4 M, F, these animals were removed from the main study), and in Group 3 F (animals from satellite study reassigned to main study). Exposure-related bw effects were observed in Groups 2 (M), 3 (F &M), and 4 (F &M). Exposure-related lung toxicity was observed. Nickel lung burden (μg Ni/lung) increased with exposure and with time (appeared to reach steady-state at 12 mo)[g]. Increases in adrenal tumours were within published (external) historical controls for Wistar rats

[a] Includes 1 squamous cell carcinoma
[b] Only alveolar bronchiolar adenomas observed in female rats; adjusted rate not reported
[c] Adjusted rates not provided
[d] Dunnick reported 1 tumour and NTP technical report reported 0
[e] Only benign tumours observed.
[f] *P*-value not reported calculated by Peto
[g] Data not available for all time points
[h] A negative trend or a lower incidence in an exposure group is indicated by N
bw, body weight; d, day or days; h, hour or hours; F, female; M male; mo, month or months; Ni, nickel; NR, not reported; vs, versus; wk, week or weeks

fibromas, malignant fibrous histiocytomas or leiomyosarcomas) were observed in male or female F344 rats administered nickel subsulfide intramuscularly (Ohmori *et al.*, 1990; Kasprzak & Ward, 1991), and intra-articularly (Ohmori *et al.*, 1990). One study found that in female rats subjected to bone fractures and treated intramuscularly or intra-articularly had a shorter time to sarcoma formation, reduced survival time, and higher metastatic rate than rats treated with nickel alone (Ohmori *et al.*, 1990). Ohmori *et al.* (1999) studied strain susceptibility in male and female Wistar rats, and one strain (CRW) was found to be more sensitive to intramuscular injection of nickel.

(c) Hamster

Nickel subsulfide induced local sarcomas after repository injections at multiple sites in numerous studies in hamsters (IARC, 1990).

(d) Rabbit

Nickel subsulfide induced local sarcomas after repository injections at multiple sites in numerous studies rabbits (IARC, 1990).

3.3.2 Nickel oxide and hydroxide

Nickel oxide induced lung tumours in rats by intratracheal instillation (Pott *et al.*, 1987), local sarcomas in mice by intramuscular injection (Gilman, 1962), and rats by intramuscular, intrapleural, and intraperitoneal injection (Gilman, 1962; Sunderman & McCully, 1983; Skaug *et al.*, 1985; Pott *et al.*, 1987). Nickel hydroxide induced local sarcomas in rats when tested by intramuscular injection (Gilman, 1966; Kasprzak *et al.*, 1983).

Sunderman *et al.* (1990) tested the carcinogenicity of five nickel oxides or nickel-copper oxides in male Fisher 344 rats. The three oxides that induced sarcomas at the injection sites had measurable dissolution rates in body fluids, and were strongly positive in an erythrocytosis stimulation assay, demonstrating nickel bioavailability.

3.3.3 Nickel acetate

(a) Mouse

Nickel acetate when administered by intraperitoneal injection induced lung adenocarcinomas and pulmonary adenomas in Strain A mice (Stoner *et al.*, 1976; Poirier *et al.*, 1984).

(b) Rat

Nickel acetate induced malignant tumours in the peritoneal cavity when administered by intraperitoneal injection in rats (Pott *et al.*, 1989, 1990).

A single intraperitoneal injection of nickel acetate initiated renal epithelial tumours (including carcinoma) after promotion using sodium barbital in the drinking-water in male rats (Kasprzak *et al.*, 1990).

See Table 3.3.

3.3.4 Metallic nickel

Intratracheal administration of metallic nickel powder caused lung tumours in rats (Pott *et al.*, 1987). Metallic nickel also caused local tumours in rats when administered by injection (intrapleural, subcutaneous, intramuscular, and intraperitoneal) (Hueper, 1952, 1955; Mitchell *et al.*, 1960; Heath & Daniel, 1964; Furst & Schlauder, 1971; Berry *et al.*, 1984; Sunderman, 1984; Judde *et al.*, 1987; Pott *et al.*, 1987, 1990).

3.3.5 Nickel sulfate

Nickel sulfate induced malignant tumours in the peritoneal cavity when administered by intraperitoneal injection in rats (Pott *et al.*, 1989, 1990).

Table 3.3 Studies of cancer in experimental animals exposed to nickel compounds (parenteral administration and intratracheal instillation)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel subsulfide				
Mouse, Strain A (M) 45 wk McNeill *et al.* (1990)	i.t. and i.p. 0, 0.53, 0.160 mg/kg bw 3 dosing regimens for 15 wk 1/wk (15 treatments), 1 every 2 wk (8 treatments), 1 every 3 wk (5 treatments); 3 doses per regiment; 30/group 10 mice sacrified after 20 wk	Lung (adenomas at 45 wk[a]): i.t.– Number of treatments: dose 5: 68%, 63%, 58% 8: 64%, 54%, 61% 15: 47%, 47%, 56% i.p.– 5: 68%, 63%, 53% 8: 58%, 53%, 63% 15: 63%, 47%, 50%		Age at start, 8–10 wk Nickel subsulfide –1.8 µm mass medium diameter 73% Nickel and 26.3% sulfur (weight) Urethane (positive control) significantly increased tumour incidence i.p., i.t., after 20 wk, and i.t. after 45 wk, average. number of adenoma/mouse increased i.p. and i.t. at both time points No treatment effects on bw
Mouse, C57BL/6, B6C3F$_1$, CeH/He (M) 78 wk Rodriguez *et al.* (1996)	i.m. (thigh) 0, 0.5, 1.0, 2.5, 5.0, 10 mg/site (single injection) 30/group	Injection site (rhabdomyosarcomas, fibrosarcomas, and other e.g. liposarcomas, haemangiosarcomas): C3He 0/30, 5/30 (16.6%), 10/30 (33.3%), 20/27 (74.1%), 28/29, (96.6%) 14/14 (100%) B6C3F$_1$ 0/30, 2/29 (6.9%), 8/30 (26.7%), 15/30 (50.0%), 16/20 (80%), 5/6 (83.3%) C57BL 0/24, 1/27 (3,7%), 4/28 (14.3%), 6/21 (28.6%), 6/15(40%), 0/2	 [$P = 0.052$, 0.5 mg; $P < 0.001$ for other doses][a] [$P < 0.01$, 1.0 mg, $P < 0.001$, 2.5, 5.0, 10 mg][a] [$P < 0.01$, 2.5, 5 mg][a]	Age at start, 6–8 wk; weight, 23–29 g High dose was lethal within 1 wk to over 50% of all 3 strains; susceptibility was C57BL > B6C3F1 > C3H Treatment-related decrease in bw was observed for C3H and B6C3F$_1$ at 2 highest doses. Tumours of the liver, lung adenomas and leukaemias were also observed, but were not increased in exposed groups compared to controls Susceptibility to tumours C3H > B6C3F$_1$ > C57BL

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, MT transgenic and wild-type (M) 104 wk Waalkes *et al.* (2004)	i.m. (both thighs) 0, 0.5, 1 mg/site (single injection) 25/group	Injection site (primarily fibrosarcomas, but also included fibromas and lymphosarcomas): WT–0/24, 5/25 (20%), 10/25 (40%) MT-Tg–0/25, 7/25 (28%), 7/24 (29%)	WT: $P < 0.05$, mid-and low dose, $P_{trend} < 0.0001$ MT-Tg: $P < 0.05$, mid-and low dose, $P_{trend} = 0.0081$ trend	Age at start, 12 wk 99.9% pure, 30 µm particles Average survival time less in MT-Tg mice than controls. Treatment-related decrease in survival in WT but not MT-Tg mice. No effect on bw No differences in injection-site tumour incidence or latency between MT-Tg and WT mice
		Lung (adenomas or adenocarcinomas): WT–6/24 (25%), 5/25 (20%), 9/25 (36%) MT-Tg–0/25, 3/25 (12%), 4/24 (17%)	MT-Tg: $P = 0.0502$ high dose $P_{trend} = 0.046$	MT-transgenic controls had significantly lower incidence of lung tumours than WT controls.
Mouse, MT-null (double knockout) and wild-type (M) 104 wk Waalkes *et al.* (2005)	i.m. (both thighs) 0, 0.5, 1 mg/site (single injection), 25/group	Injection site (primarily fibrosarcomas, but also included fibromas): WT–0/24, 8/25(32.0%), 18/25 (72.0%) MT-null–0/24, 11/24 (45.8%), 15/23 (62.5%) Lung (adenomas or adenocarcinomas): WT–7/24 (29.2%), 12/25 (48.0%), 11/25 (44.0%) MT-null–10/24 (41.7%), 13/24 (54.2%), 4/23 (16.7%)	$P < 0.05$ low and high dose $P < 0.05$ low and high dose	Age at start, 12 wk 99.9% pure, < 30 µm particles No difference in survival between control MT-null mice and control WT mice. Nickel treatment reduced survival at later time points corresponding to the appearance of sarcomas. Nickel treatment reduced bw in high-and mid dose MT-null and high-dose WT mice

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, MT-null (double knockout) and wild-type (M) 104 wk Waalkes *et al.* (2005) (contd.)		Lung (adenocarcinomas): WT–1/24 (4.2%), 10/25 (40.0%), 3/25 (12.0%) MT-null–3/24 (12.5%), 3/24 (12.5%), 4/23 (17.4%)	 WT: $P < 0.05$ low dose	
		Lung (adenomas): WT–6/24 (25%), 2/25 (8.0%), 8/25 (32.0%) MT-null–7/24 (29.2%), 10/24 (41.7%), 0/23	 MT-null: $P < 0.05$ control vs high dose	
Rat, F344/NCr (M) 109 wk Kasprzak *et al.* (1994)	i.r. (2 injections) Ni_3S_2 – 5 mg, MgCarb –6.2 mg, Fe^0–3.4 mg Groups: treatment, number of animals Group 1: Ni_3S_2, 40 Group 2: Ni_3S_2 + MgCarb, 20 Group 3: MgCarb, 20 Group 4: Ni_3S_2+ Fe^0, 20 Group 5: Fe^0, 20 Group 6: vehicle, 20 20–40/group	Kidney (malignant tumours of mesenchymal cell origin) at 104 wk: Group 1: 25/40 (63%) Group 2: 4/20 (20%) Group 3: 0/20 Group 4: 12/20 (60%) Group 5: 0/20 Group 6: 0/20	 Group 2 vs Group 1 [$P < 0.01$][a]	Ni_3S_2 < 10µm No effect on bw or survival (from causes other than kidney tumours) MgCarb also delayed onset of tumours (besides decreasing the incidence), and Fe decreased time until first tumour Metastases to lung, liver, spleen and other kidney

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344/NCr (M) 109 wk Kasprzak & Ward (1991)	i.m. and s.c (single injection) Ni_3S_2– 2.5 mg, MB – 0.5 mg, CORT–1.0 mg, IND –1.0 mg. Groups: i.m., s.c., number of animals Group 1: Ni_3S_2, none, 20 Group 2: MB, none, 20 Group 3: Ni_3S_2+ MB, none, 20 Group 4: CORT, none, 20 Group 5: Ni_3S_2+ CORT, none, 20 Group 6: IND, none, 20 Group 7: Ni_3S_2+ IND, none, 20 Group 8: water, none, 20 Group 9: Ni_3S_2, MB, 20 Group 10: Ni_3S_2, IND, 20 20/group	Injection-site tumours (rhabdomosarcomas, fibrosarcomas, histolytic sarcomas): 36 wk; 71 wk Group 1: 10/20 (50%); 17/20 (85%) Group 2: 0/20; 0/20 Group 3:0/20; 1/20 (5%) Group 4: 0/20; 0/20 Group 5: 9/20 (45%); 17/20 (85%) Group 6: 0/20; 0/20 Group 7: 6/20 (30%); 16/20 (80%) Group 8: 0/20; 0/20 Group 9: 18/20 (90%); 20/20 (100%) Group 10: 13/20 (65%); 19/20 (95%)	[Groups 2, 3, 4, 6 or 8 vs Group 1, 36 & 71 wk, $P < 0.01$; Group 9 vs Group 1, 36 wk, $P < 0.05$][a]	Age at start, 8 wk $Ni_3S_2 < 10 \mu m$ No effect on bw Metastases to the lung MB given away from the injection site (s.c.) decreased tumour latency induced by Ni_3S

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (F) 1 yr Ohmori *et. al.* (1990)	Ni_3S_2–10 mg Groups, treatment, number of animals Group 1: fracture bone, 10 mg/fracture, 20 Group 2: 10 mg i.m right thigh, 20 Group 3: 10 mg i.a. right knee joint, 20 Group 4: control (CM), 3 fractured bone, 3 i.m., 2 i.a. 20/group	Injection site (malignant fibrous histiocytomas, rhabdomyosarcomas, fibrosarcomas, leiomyosarcomas): Group 1: 17/20 (85%) Group 2: 20/20 (100%) Group 3: 16/20 (80%) Group 4: 0/7 (0%) Metastasis (lymph node, lung): Group 1: 16/17 (94.1), 9/17 (52.9) Group 2: 5/20 (25.0%), 3/20 (15.0%) Group 3: 3/16 (18.8%), 2/16 (12.5%) Group 4: 0/7, 0/7	$P < 0.05$, Group 1 vs Group 2 or Group 3	Age at start, 10 wk Ni_3S_2 medium particle diameter < 2µm Vehicle, CM Tumour-induction time and survival time shorter in Group 1 than Groups 2 or 3. No osteogenic sarcoma developed in bone-fracture group
Rat, Wistar (M, F) 70 wk Ohmori *et al.* (1999)	Ni_3S_2–10 mg i.m. (single injection) Groups, strain, treatment; number of animals Group 1: SHR–10 mg; 15F, 15M Group 2: CWR–10 mg; 15F, 16M Group 3: SHR–0 mg; 6F, 6M Group 4: CWR–0 mg 7F, 7M 6–15/group	Sarcomas (rhabdomyosarcomas, leiomyosarcomas, fibrosarcomas and malignant fibrous histiocytomas): Groups: F; M; Total Group 1: 2/15 (13.3%); 5/15 (33.3%); 7/30 (23.3%) Group 2: 8/15 (53.3%), 13/16 (81.4%); 21/31 (67.7%) Group 3: 0/6, 0/6 Group 4: 0/7, 0/7	Total: Group 1 vs Group 2, $P < 0.005$	Age, 10 wk Ni_3S_2 medium particle diameter < 2µm Vehicle, CM Tumour incidence, progression (as shown by tumour size and metastasis) was significantly lower in SHR rats (M, F combined) than in CWR rats Metastases observed in the lung and lymph node

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel oxide				
Rat, F344 (M) 104 wk Sunderman *et al.* (1990)	i.m. (hind limb) single injection Group: Ni by wt.; other elements V: vehicle control (glycerol) A: 0.81% Ni (III); none B: 0.05% Ni (III); none F: < 0.03% Ni (III); none H: 21% Cu, 2% Fe, 1.1% Co, 1% S, 0.5% Ni_3S_2 I: 13% Cu, 1.2% Fe, 1.0 Co, 0.3% S, 1.0% Ni_3S_2 (positive control) 20 mg Ni/rat 15/group	Injection site (rhabdomyosarcomas, fibrosarcomas, malignant fibrous histiocytomas, leiomyosarcomas, undifferentiated): V, 0/15; A, 6/15 (40.0%); B, 0/15; F, 0/15; H, 13/15 (86.7%); I, 15/15 (100%) Positive control, Ni_3S_2 15/15(100%) **Metastases** V: 0, A: 3; B: 0; F: 0; H: 4; I: 4 Ni_3S_2: 12 **Other primary tumours** V: 0; A: 0; B: 3; F: 0; H: 0; I: 3 Ni_3S_2: 0	$P < 0.01$ A; $P < 0.001$ H, I, Ni_3S_2	Age at start, ~2 mo 5 NiO compounds – all compounds had 52–79% Nickel (total), and 22–24% O. Nickel could not be determined in Groups H and I because of the presence of sulfur Groups A, H, and I all had measurable dissolution rates in body fluids and were strongly positive in an erythrocytosis-stimulation assay Compounds B and F were insoluble in body fluids, did not stimulate erythrocytosis and had little Ni (III), Cu Fe, Co, or S
Rat, Wistar (F) Life span Pott *et al.* (1987)	(mg x wk) number of animals NiO 50 mg (10 × 5); 34 150 mg (10 × 15); 37 Ni_3S_2 0.94 mg (15 × 0.063); 47 1.88 mg (15 × 0.125); 45 3.75 mg (15 × 0.25); 47 Nickel powder 6 mg (20 × 0.3); 32 9 mg (10 × 0.9); 32 32–47/group	Lung (adenomas, adenocarcinomas, squamous cell carcinomas): % tumours for each dose NiO–27%, 31.6% Ni_3S_2–15%, 28.9% Nickel powder–25.6%, 25% Saline, 0%		Age at start, 11 wk NiO, 99.9% pure

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel acetate				
Rat, F344/NCr (M) 101 wk Kasprzak *et al.* (1990)	NiAcet –90 µmol/kg bw single i.p. injection NaBB–50 ppm in drinking-water (2 wk after NiAcet) Groups, treatment, # of animals Group 1: NiAcet, 23 Group 2: NiAcet + NaBB, 24 Group 3: NaBB, 24 Group 4: Saline, 24 24/group	Renal cortical tumours (adenomas & adenocarcinomas): Group 1–1/23 (4.3%) Group 2–16/24 (66.7%) (4 carcinomas) Group 3–6/24 (25%) Group 4–0/24 Renal pelvic tumours (papillomas & carcinomas): Group 1–0/23 Group 2–8/24 (33.3%) Group 3–13/24 (54.2%) (1 carcinoma) Group 4–0/24	$P < 0.008$ vs Group 3	Age at start, 5 wk Initiation/promotion study Decreased survival and bw in rats given nickel acetate followed by NaBB Kidney weight increased in Groups 2 and 3 Renal cortical tumours: metastatic nodules observed in the lung, spleen and liver
Mouse, Strain A (M, F) 30 wk Stoner *et al.* (1976)	i.p. Nickel acetate 3×/wk (24 injections total) 0, 72, 180, 360 mg/kg Saline control 20/group	Lung (adenomas): Average number of tumours/mouse (mean ± SD) Saline: 0.42 ± 0.10 72: 0.67 ± 0.16 180: 0.71 ± 0.19 360: 1.26 ± 0.29	$P < 0.01$ high dose	Age at start, 6–8 wk 99.9% pure Sample of nodules confirmed by histopathology No difference in control M, F, so M, F were combined Positive control urethane Control saline Doses correspond to MTD, ½ MTD, 1/5 MTD
Mouse, Strain A (M, F) 30 wk Poirier *et al.* (1984)	i.p. Nickel acetate 10.7 mg/kg bw (0.04 mmol kg/bw)/injection 3×/wk (24 injections total) 30/group/sex	Lung (adenomas): Average number of tumours/mouse (mean ± SD) Saline: 0.32 ± 0.12 Nickel acetate: 1.50 ± 0.46	$P < 0.05$	Age at start, 6–8 wk Nodules (sample) confirmed by histology Co-exposure to calcium and magnesium decreased multiplicity

[a] Calculated by Fisher Exact Test, Significance not reported by authors

bw, body weight; CM, chloromycetin; CORT, cortisol; CWR, common closed colony rats; F, female; Fe^0, metallic iron; HSR, spontaneously hypertensive rats; i.a., intra-articular; i.f., intra-fat; i.m., intramuscular; IND, indometacin; i.p., intraperitoneal; i.r., intrarenal; i.t., intratracheal instillation; M, male; MB, *Mycobacterium bovis* antigen; MgCarb, magnesium basic carbonate; MT, metallothionien; MTD, maximum tolerated dose; NABB, sodium barbital; Ni, nickel; NiAcet, nickel acetate; Ni_3S, nickel subsulfide; s.c., subcutaneous; SD, standard deviation; Tg, Transgenic; wk, week or weeks; WT, wild type; yr, year or years

3.3.6 Nickel chloride

Nickel chloride induced malignant tumours in the peritoneal cavity when administered by intraperitoneal injection in rats (Pott *et al.*, 1989, 1990).

3.3.7 Other forms of nickel

Intramuscular administration of nickel sulfarsenide, nickel arsenides, nickel antimonide, nickel telluride, and nickel selenides caused local sarcomas in rats (Sunderman & McCully, 1983). Intramuscular administration of nickelocene caused some local tumours in rats and hamsters (Furst & Schlauder, 1971).

3.4 Transplacental exposure

3.4.1 Nickel acetate

Diwan *et al.* (1992) studied the carcinogenic effects of rats exposed transplacentally to nickel acetate and postnatally to sodium barbital in drinking-water. Pregnant F344 were given nickel acetate by intraperitoneal injection, and their offspring were divided into groups receiving either tap water or sodium barbital in drinking-water. An increased incidence in pituitary tumours was observed in the offspring of both sexes transplacentally exposed to nickel acetate. These tumours were mainly malignant, and are rare tumours. Renal tumours were observed in the male offspring exposed transplacentally to nickel acetate, and receiving sodium barbital postnatally, but not in the male offspring receiving tap water after nickel *in utero*.

See Table 3.4.

3.5 Synthesis

The inhalation of nickel oxide, nickel subsulfide, and nickel carbonyl caused lung tumours in rats. Intratracheal instillation of nickel oxide, nickel subsulfide, and metallic nickel caused lung tumours in rats. Lung tumours were observed by the intraperitoneal injection of nickel acetate in two studies in A/J mice, and by intramuscular injection of nickel subsulfide in mice. The inhalation of nickel oxide, nickel subsulfide, and metallic nickel caused adrenal medulla pheochomocytoma in rats. Transplacental nickel acetate induced malignant pituitary tumours in the offspring in rats. Several nickel compounds (nickel oxides, nickel sulfides, including nickel subsulfide, nickel sulfate, nickel chloride, nickel acetate, nickel sulfarsenide, nickel arsenide, nickel antimonide, nickel telluride, nickel selenide, nickelocene, and metallic nickel) administered by repository injection caused sarcomas in multiple studies. The inhalation of metallic nickel did not cause lung tumours in rats. The inhalation and oral exposure to nickel sulfate did not cause tumours in rats or mice. The inhalation of nickel subsulfite did not cause tumours in mice.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

In rodents, nickel salts and nickel sulfides are absorbed through the lungs and excreted mainly in the urine (Benson *et al.*, 1994, 1995a). After inhalation exposure to green nickel oxide, nickel is not distributed in extrapulmonary tissues, and is excreted only in faeces (Benson *et al.*, 1994). In humans, soluble nickel compounds are rapidly absorbed through the lungs, and excreted in the urine. After inhalation exposure to insoluble nickel species, elevated concentrations of nickel are observed in the plasma and urine, but the absorption is slow (Bernacki *et al.*, 1978; Tola *et al.*, 1979).

In rats exposed to nickel sulfate hexahydrate by inhalation for 6 months or 2 years,

Table 3.4 Studies of cancer in experimental animals exposed to nickel acetate (transplacental exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Results Target organs	Significance	Comments
Rat, F344/NCr (M, F) 85 wk Diwan *et al.* (1992)	*Dams – i.p* NiAcet (90 µmol/kg wt total) Group:/µmol/kg bw; regimen Group 1: 90; once at Day 17 of gestation Group 2: 45; twice at Days 16 & 18 of gestation Group 3: 45; 4 times at Days 12, 14, 16, 18 of gestation Group 4: control (180 NaAcet) once at Day 18 of gestation *Offspring 4 to 85 wk (drinking-water)* ad libitum 1A, 2A, 4A – tap water 1B, 2B, 4B – 0.05% NBB	Renal tumours (cortex adenomas and carcinomas; or pelvis papillomas and carcinomas): 1A: 0/17 (M), 0/16 (F) 2A: 0/15 (M), 0/15 (F) 4A: 0/15 (M), 0/16 (F) 1B: 8/15 (53.3%, M), 0/15 (F) 2B: 7/15 (46.7%, M), 0/15 (F) 4B: 1/15 (6.67%, M), 0/14 (F) Pituitary gland (adenomas or carcinomas): 1A: 9/17 (52.9%, M), 5/16 (31.3%, F), 14/33 (42.3%, M, F) 2A: 6/15 (40.0%, M), 8/16 (50%, F), 14/31 (45.2%, M, F) 4A: 1/15 (6.7%, M), 3/14 (21.4%, F) 1B: 6/15 (40.0%, M), 5/15 (33.3%, F) 2B: 7/15 (46.7%, M), 6/15 (40.0%, F) 4B: 2/15 (13.3%, M), 4/14 (28.6%, F)	 M: $P = 0.007$ (1B vs 4B) M: $P = 0.012$ (2B vs 4B) M, F: $P = 0.12$ 1A vs 4A M, F: $P = 0.008$ 2A vs 4A	Dams, age at start 3–4 mo Purity not provided Male (Groups 1 & 2) – significantly decreased bw at 75 wk All offspring in Group 3 died at 72 h. Survival was decreased in Groups 1A, 1B, 2A and 2B compared to controls (4A and 4B) Pituitary tumours: significantly decreased latency for Groups 1A (M, F), 1B (M, F) and 2A (F) compared to the Groups 4A or 4B (corresponding M or F)

h, hour or hours; F, female; i.p., intraperitoneal; M, male; mo, month or months; NaBB, sodium barbital; vs, versus; wk, week or weeks

no pulmonary accumulation is observed; in a similar exposure scenario with nickel subsulfide, concentrations of nickel are detected in the lungs, with very slight nickel accumulation. Following the exposure of green nickel oxide to rats, the nickel lung clearance half-life is approximately 130 days, and in long-term exposure (NTP, 1996a, b, c; described in Section 3), a remarkable accumulation of nickel is observed (Benson *et al.*, 1995b; Dunnick *et al.*, 1995). The lung clearance half-life of nanoparticulate black nickel oxide in rats is reported as 62 days (Oyabu *et al.*, 2007). The difference in the two clearance rates may be related to the greater water solubility (and the smaller particle size) of the nanoparticulate black nickel oxide. In mice, the observed clearance for nickel sulfate is fast, but for nickel subsulfide intermediate and for green nickel oxide, very slow (Dunnick *et al.*, 1995).

4.1.1 Cellular uptake

Nickel chloride has been shown in different cell lines in culture to be transported to the nucleus (Abbracchio *et al.*, 1982; Edwards *et al.*, 1998; Ke *et al.*, 2006, 2007; Schwerdtle & Hartwig, 2006). Soluble nickel chloride compounds enter cells via the calcium channels and by metal ion transporter 1 (Refsvik & Andreassen, 1995; Funakoshi *et al.*, 1997; Gunshin *et al.*, 1997; Garrick *et al.*, 2006). Crystalline nickel sulfides are phagocytized by a large variety of different cells in culture (Kuehn *et al.*, 1982; Miura *et al.*, 1989; Hildebrand *et al.*, 1990, 1991; IARC, 1990).

Black nickel oxide and nickel chloride are taken up by human lung carcinoma cell lines A549 in culture; the nucleus/cytoplasm ratio is > 0.5 for black nickel oxide, and < 0.18 for nickel chloride (Fletcher *et al.*, 1994; Schwerdtle & Hartwig, 2006).

After phagocytosis of nickel subsulfide, intracellular nickel containing particles rapidly dissolve, and lose sulfur (Arrouijal *et al.*, 1990; Hildebrand *et al.*, 1990, 1991; Shirali *et al.*, 1991).

4.2 Genetic and related effects

The mechanisms of the carcinogenicity of nickel compounds have been reviewed extensively (Hartwig *et al.*, 2002; Zoroddu *et al.*, 2002; Costa *et al.*, 2003, 2005; Harris & Shi, 2003; Kasprzak *et al.*, 2003; Lu *et al.*, 2005; Durham & Snow, 2006; Beyersmann & Hartwig, 2008; Salnikow & Zhitkovich, 2008).

Based on the uptake and distribution in cells described above, the ultimate genotoxic agent is Ni (II). However, direct reaction of Ni (II) with DNA does not seem to be relevant under realistic exposure conditions. Nevertheless, nickel is a redox-active metal that may, in principle, catalyse Fenton-type reactions, and thus generate reactive oxygen species (Nackerdien *et al.*, 1991; Kawanishi *et al.*, 2001). Genotoxic effects have been consistently observed in exposed humans, in experimental animals, and in cell culture systems, and include oxidative DNA damage, chromosomal damage, and weak mutagenicity in mammalian cells. These effects are likely to be due to indirect mechanisms, as described in detail below.

4.2.1 Direct genotoxicity

(a) DNA damage

Water-soluble as well as water-insoluble nickel compounds induce DNA strand breaks and DNA protein crosslinks in different mammalian test systems, including human lymphocytes. Nevertheless, in the case of DNA strand breaks and oxidative DNA lesions, these events mainly occur with conditions that involve comparatively high cytotoxic concentrations (IARC, 1990; Pool-Zobel *et al.*, 1994; Dally & Hartwig, 1997; Cai & Zhuang, 1999; Chen *et al.*, 2003; M’Bemba-Meka *et al.*, 2005; Schwerdtle & Hartwig, 2006; Caicedo *et al.*, 2007). This is also true for the induction of oxidative DNA base modifications in cellular systems. Nevertheless, oxidative DNA damage is also observed in experimental animals, this may

be due to repair inhibition of endogenous oxidative DNA damage.

The intratracheal instillation of several soluble and insoluble nickel compounds to rats significantly increases 8-hydroxydeoxyguanine (8-OH-dG) content in the lungs. Concomitantly, microscopic signs of inflammation in the lungs are also observed. Two distinct mechanisms are proposed: one via an inflammatory reaction and the other through cell-mediated reactive oxygen species formation (Kawanishi *et al.*, 2001; Kawanishi *et al.*, 2002).

(b) Chromosomal alterations

Water-soluble and poorly water-soluble nickel compounds induce sister chromatid exchange and chromosomal aberrations at toxic levels in different mammalian test systems (Conway *et al.*, 1987; Conway & Costa, 1989; IARC, 1990; Howard *et al.*, 1991). Chromosomal aberrations are most pronounced in heterochromatic chromosomal regions (Conway *et al.*, 1987). Water-soluble and poorly water-soluble nickel compounds induce micronuclei at comparatively high concentrations. Because increases in both kinetochore-positive and -negative micronuclei are observed, these effects are likely due to aneugenic as well as clastogenic actions (Arrouijal *et al.*, 1990, 1992; Hong *et al.*, 1997; Seoane & Dulout, 2001). The induction of chromosomal aberrations and micronuclei in rodents treated with different nickel compounds is not consistent across studies (Sobti & Gill, 1989; Arrouijal *et al.*, 1990; Dhir *et al.*, 1991; IARC, 1990; Oller & Erexson, 2007). Enhanced frequencies of chromosomal aberrations were observed in some studies in lymphocytes of nickel-exposed workers (IARC, 1990).

(c) Gene mutations in bacterial and mammalian test systems

Nickel compounds are not mutagenic in bacterial test systems, and are only weakly mutagenic in cultured mammalian cells. Even though, mutagenic responses for both water-soluble and water-insoluble nickel compounds have been reported in transgenic G12 cells, this effect was later shown to result from epigenetic gene-silencing (Lee *et al.*, 1995). Nevertheless, the prolonged culture of V79 cells after treatment with nickel sulfate results in the appearance of genetically unstable clones with high mutation rates together with chromosomal instability (Little *et al.*, 1988; Ohshima, 2003).

(d) Cell transformation

Water-soluble and poorly water-soluble nickel compounds induced anchorage-independent growth in different cell systems (IARC, 1990), including the mouse-embryo fibroblast cell-line PW and the human osteoblast cell line HOS-TE85 (Zhang *et al.*, 2003). Nickel compounds were shown to cause morphological transformation in different cell types (Conway & Costa, 1989; Miura *et al.*, 1989; Patierno *et al.*, 1993; Lin & Costa, 1994).

4.2.2 Indirect effects related to genotoxicity

As stated above, the direct interaction of nickel compounds with DNA appears to be of minor importance for inducing a carcinogenic response. However, several indirect mechanisms have been identified, which are discussed below.

(a) Oxidative stress

Treatment with soluble and insoluble nickel causes increases in reactive oxygen species in many cell types (Huang *et al.*, 1993; Salnikow *et al.*, 2000; Chen *et al.*, 2003).

Increased DNA stand breaks, DNA–protein crosslinks and sister chromatid exchange are found in cells treated with soluble and insoluble nickel compounds, and these are shown to result from the increase in reactive oxygen species (Chakrabarti *et al.*, 2001; Błasiak *et al.*, 2002; Woźniak & Błasiak, 2002; M'Bemba-Meka *et al.*, 2005, 2007).

Intraperitoneal injection of nickel acetate in rat did not cause any DNA damage in liver and kidney at 12 hours. However, oxidative DNA damage increased after 24 hours, and persisted in the kidney for 14 days (Kasprzak *et al.*, 1997).

(b) Inhibition of DNA repair

The treatment of cells with soluble Ni (II) increases the DNA damage and the mutagenicity of various agents (Hartwig & Beyersmann, 1989; Snyder *et al.*, 1989; Lee-Chen *et al.*, 1993).

Soluble Ni (II) inhibits nucleotide-excision repair after UV irradiation, and the effect seems to be on the incision, the polymerization, and ligation steps in this pathway (Hartwig *et al.*, 1994; Hartmann & Hartwig, 1998; Woźniak & Błasiak, 2004). One of the proteins in nucleotide-excision repair, the XPA protein, may be a target of Ni (II) (Asmuss *et al.*, 2000a, b).

Soluble nickel chloride also inhibits base-excision repair. The base-excision repair enzyme, 3-methyladenine-DNA glycosylase II, is inhibited specifically (Dally & Hartwig, 1997; Woźniak & Błasiak, 2004; Wang *et al.*, 2006).

There is some evidence that the enzyme O^6-methylguanine-DNA methyltransferase (MGMT) is inhibited by nickel chloride (Iwitzki *et al.*, 1998).

(c) Epigenetic mechanisms

Both water-soluble and water-insoluble nickel compounds are able to cause gene silencing (Costa *et al.*, 2005). This effect was first found when "mutations" in the transgenic *gpt* gene in G12 cells were found to be epigenetically silenced rather than mutated (Lee *et al.*, 1995). Genes that are located near heterochromatin are subject to such inactivation by nickel. The *gpt* gene was silenced by DNA methylation. Additional studies show that cells treated with nickel have decreased histone acetylation, and altered histone methylation patterns (Golebiowski & Kasprzak, 2005; Chen *et al.*, 2006). Nickel also causes ubiquination and phosphorylation of histones (Karaczyn *et al.*, 2006; Ke *et al.*, 2008a, b). Permanent changes in gene expression are important in any mechanism of carcinogenesis.

4.3 Synthesis

The ultimate carcinogenic species in nickel carcinogenesis is the nickel ion Ni (II). Both water-soluble and poorly water-soluble nickel species are taken up by cells, the former by ion channels and transporters, the latter by phagocytosis. In the case of particulate compounds, nickel ions are gradually released after phagocytosis. Both water-soluble and -insoluble nickel compounds result in an increase in nickel ions in the cytoplasm and the nucleus. Nickel compounds are not mutagenic in bacteria, and only weakly mutagenic in mammalian cells under standard test procedures, but can induce DNA damage, chromosomal aberrations, and micronuclei *in vitro* and *in vivo*. However, delayed mutagenecity and chromosomal instability are observed a long time after treatment of cells with nickel. Nickel compounds act as co-mutagens with a variety of DNA-damaging agents. Thus, disturbances of DNA repair appear to be important. A further important mechanism is the occurrence of epigenetic changes, mediated by altered DNA methylation patterns, and histone modification. Inflammation may also contribute to nickel-induced carcinogenesis.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of mixtures that include nickel compounds and nickel metal. The evidence is strongest for soluble nickel compounds; there is also independent evidence for the carcinogenicity of oxidic and sulfidic nickel compounds. These agents cause cancers of the lung and of the nose and nasal sinuses.

There is *sufficient evidence* in experimental animals for the carcinogenicity of nickel monoxides, nickel hydroxides, nickel sulfides (including nickel subsulfide), nickel acetate, and nickel metal.

There is *limited evidence* in experimental animals for the carcinogenicity of nickelocene, nickel carbonyl, nickel sulfate, nickel chloride, nickel arsenides, nickel antimonide, nickel selenides, nickel sulfarsenide, and nickel telluride.

There is *inadequate evidence* in experimental animals for the carcinogenicity of nickel titanate, nickel trioxide, and amorphous nickel sulfide.

In view of the overall findings in animals, there is *sufficient evidence* in experimental animals for the carcinogenicity of nickel compounds and nickel metal.

Nickel compounds are *carcinogenic to humans (Group 1)*.

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ASBESTOS (CHRYSOTILE, AMOSITE, CROCIDOLITE, TREMOLITE, ACTINOLITE, AND ANTHOPHYLLITE)

Asbestos was considered by previous IARC Working Groups in 1972, 1976, and 1987 (IARC, 1973, 1977, 1987a). Since that time, new data have become available, these have been incorporated in the *Monograph*, and have been taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

Asbestos is the generic commercial designation for a group of naturally occurring mineral silicate fibres of the serpentine and amphibole series. These include the serpentine mineral chrysotile (also known as 'white asbestos'), and the five amphibole minerals – actinolite, amosite (also known as 'brown asbestos'), anthophyllite, crocidolite (also known as 'blue asbestos'), and tremolite (IARC, 1973; USGS, 2001). The conclusions reached in this *Monograph* about asbestos and its carcinogenic risks apply to these six types of fibres wherever they are found, and that includes talc containing asbestiform fibres. Erionite (fibrous aluminosilicate) is evaluated in a separate *Monograph* in this volume.

Common names, Chemical Abstracts Service (CAS) Registry numbers and idealized chemical formulae for the six fibrous silicates designated as 'asbestos' are presented in Table 1.1. Specific chemical and physical properties are also presented.

1.2 Chemical and physical properties of the agent

The silicate tetrahedron (SiO_4) is the basic chemical unit of all silicate minerals. The number of tetrahedra in the crystal structure and how they are arranged determine how a silicate mineral is classified.

Serpentine silicates are classified as 'sheet silicates' because the tetrahedra are arranged to form sheets. Amphibole silicates are classified as 'chain silicates' because the tetrahedra are arranged to form a double chain of two rows aligned side by side. Magnesium is coordinated with the oxygen atom in serpentine silicates. In amphibole silicates, cationic elements such as aluminium, calcium, iron, magnesium, potassium, and sodium are attached to the tetrahedra. Amphiboles are distinguished from one another by their chemical composition. The chemical formulas of asbestos minerals are idealized. In

Table 1.1 Common names, CAS numbers, synonyms, non-asbestos mineral analogues, idealized chemical formulae, selected physical and chemical properties of asbestos minerals

Common Name	CAS No.	Synonyms	Non-Asbestos Mineral Analogue	Idealized Chemical Formula	Colour	Decom-position Tempe-rature (°C)	Other Properties
Asbestos	1332-21-4*	Unspecified		Unspecified			
Serpentine group of minerals							
Chrysotile	12001-29-5*	Serpentine asbestos; white asbestos	Lizardite, antigorite	$[Mg_3Si_2O_5(OH)_4]_n$	White, grey, green, yellowish	600–850	Curled sheet silicate, hollow central core; fibre bundle lengths = several mm to more than 10 cm; fibres more flexible than amphiboles; net positive surface charge; forms a stable suspension in water; fibres degrade in dilute acids
Amphibole group of minerals							
Crocidolite	12001-28-4*	Blue asbestos	Riebeckite	$[NaFe^{2+}{}_3Fe^{3+}{}_2Si_8O_{22}(OH)_2]_n$	Lavender, blue green	400–900	Double chain silicate; shorter, thinner fibres than other amphiboles, but not as thin as chrysotile; fibre flexibility: fair to good; spinnability: fair; resistance to acids: good; less heat resistance than other asbestos fibres; usually contains organic impurities, including low levels of PAHs; negative surface charge in water
Amosite	12172-73-5*	Brown asbestos	Grunerite	$[(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2]_n$	Brown, grey, greenish	600–900	Double chain silicate; long, straight, coarse fibres; fibre flexibility: somewhat; resistance to acids: somewhat; occurs with more iron than magnesium; negative surface charge in water
Antho-phyllite	17068-78-9*	Ferroantho-phyllite; azbolen asbestos	Antho-phyllite	$[(Mg, Fe^{2+})_7Si_8O_{22}(OH)_2]_n$	Grey, white, brown-grey, green	NR	Double chain silicate; short, very brittle fibres; resistance to acids: very; relatively rare; occasionally occurs as contaminant in talc deposits; negative surface charge in water
Actinolite	12172-67-7*	Unspecified	Actinolite	$[Ca_2(Mg, Fe^{2+})_5Si_8O_{22}(OH)_2]_n$	Green	NR	Double chain silicate; brittle fibres; resistance to acids: none; occurs in asbestiform and non-asbestiform habit; iron-substituted derivative of tremolite; common contaminant in amosite deposits; negative surface charge in water
Tremolite	14567-73-8*	Silicic acid; calcium magnesium salt (8:4)	Tremolite	$[Ca_2Mg_5Si_8O_{22}(OH)_2]_n$	White to pale green	950–1040	Double chain silicate; brittle fibres; acid resistant; occurs in asbestiform and non-asbestiform habit; common contaminant in chrystotile and talc deposits; negative surface charge in water

* identified as asbestos by CAS Registry
NR, not reported
From ATSDR (2001), USGS (2001), HSE (2005), NTP (2005)

natural samples, the composition varies with respect to major and trace elements (USGS, 2001; HSE, 2005). More detailed information on the chemical and physical characteristics of asbestos – including atomic structure, crystal polytypes, fibre structure, chemistry and impurities – can be found in the previous *IARC Monograph* (IARC, 1973).

The structure of silicate minerals may be fibrous or non-fibrous. The terms 'asbestos' or 'asbestiform minerals' refer only to those silicate minerals that occur in polyfilamentous bundles, and that are composed of extremely flexible fibres with a relatively small diameter and a large length. These fibre bundles have splaying ends, and the fibres are easily separated from one another (USGS, 2001; HSE, 2005). Asbestos minerals with crystals that grow in two or three dimensions and that cleave into fragments, rather than breaking into fibrils, are classified as silicate minerals with a 'non-asbestiform' habit. These minerals may have the same chemical formula as the 'asbestiform' variety. (NIOSH, 2008).

Chrysotile, lizardite, and antigorite are the three principal serpentine silicate minerals. Of these, only chrysotile occurs in the asbestiform habit. Of the amphibole silicate minerals, amosite and crocidolite occur only in the asbestiform habit, while tremolite, actinolite and anthophyllite occur in both asbestiform and non-asbestiform habits (USGS, 2001; HSE, 2005; NTP, 2005).

Historically, there has been a lack of consistency in asbestos nomenclature. This frequently contributed to uncertainty in the specific identification of asbestos minerals reported in the literature. The International Mineralogical Association (IMA) unified the current mineralogical nomenclature under a single system in 1978. This system was subsequently modified in 1997 (NIOSH, 2008).

Asbestos fibres tend to possess good strength properties (e.g. high tensile strength, wear and friction characteristics); flexibility (e.g. the ability to be woven); excellent thermal properties (e.g. heat stability; thermal, electrical and acoustic insulation); adsorption capacity; and, resistance to chemical, thermal and biological degradation (USGS, 2001; NTP, 2005).

1.3 Use of the agent

Asbestos has been used intermittently in small amounts for thousands of years. Modern industrial use dates from about 1880, when the Quebec chrysotile fields began to be exploited. During the next 50 years gradual increases in production and use were reported with a cumulative total of somewhat less than 5000 million kg mined by 1930 (IARC, 1973).

As described above, asbestos has several chemical and physical properties that make it desirable for a wide range of industrial applications. By the time industrial and commercial use of asbestos peaked, more than 3000 applications or types of products were listed (NTP, 2005). Production and consumption of asbestos has declined in recent years due to the introduction of strict regulations governing exposure and/or outright bans on exposure.

Asbestos is used as a loose fibrous mixture, bonded with other materials (e.g. Portland cement, plastics and resins), or woven as a textile (ATSDR, 2001). The range of applications in which asbestos has been used includes: roofing, thermal and electrical insulation, cement pipe and sheets, flooring, gaskets, friction materials (e.g. brake pads and shoes), coating and compounds, plastics, textiles, paper, mastics, thread, fibre jointing, and millboard (USGS, 2001; NTP, 2005; Virta, 2006). Certain fibre characteristics, such as length and strength, are used to determine the most appropriate application. For example, longer fibres tend to be used in the production of textiles, electrical insulation, and filters; medium-length fibres are used in the production of asbestos cement pipes and sheets, friction materials (e.g. clutch facings, brake linings), gaskets, and pipe coverings; and,

short fibres are used to reinforce plastics, floor tiles, coatings and compounds, and roofing felts (NTP, 2005).

Since peaking in the 1970s, there has been a general decline in world production and consumption of asbestos. Peak world production was estimated to be 5.09 million metric tons in 1975, with approximately 25 countries producing asbestos and 85 countries manufacturing asbestos products (USGS, 2001; Nishikawa *et al.*, 2008). Worldwide 'apparent consumption' of asbestos (calculated as production plus imports minus exports) peaked at 4.73 million metric tons in 1980. Asbestos cement products are estimated to have accounted for 66% of world consumption in that year (Virta, 2006). In the USA, consumption of asbestos peaked in 1973 at 719000 metric tons (USGS, 2001).

Historical trends worldwide in per capita asbestos use are presented in Table 1.2, and peak use of asbestos was higher and occurred earlier in the countries of Northern and western Europe, Oceania, and the Americas (excluding South America). Very high asbestos use was recorded in Australia (5.1 kg per capita/year in the 1970s), Canada (4.4 kg per capita/year in the 1970s), and several countries of Northern and western Europe (Denmark: 4.8 kg per capita/year in the 1960s; Germany: 4.4 kg per capita/year in the 1970s; and Luxembourg: 5.5 kg per capita/year in the 1960s) (Nishikawa *et al.*, 2008).

Current use of asbestos varies widely. While some countries have imposed strict regulations to limit exposure and others have adopted bans, some have intervened less, and continue to use varying quantities of asbestos (Table 1.2). According to recent estimates by the US Geological Survey, world production of asbestos in 2007 was 2.20 million metric tonnes, slightly increased from 2.18 million metric ton in 2006. Six countries accounted for 96% of world production in 2006: the Russian Federation (925000 metric tons), the People's Republic of China (360000 metric tons), Kazakhstan (300000 metric tons), Brazil (227304 metric tons), Canada (185000 metric tons), and Zimbabwe (100000 metric tons) (Virta, 2008). During 2000–03, asbestos consumption increased in China, India, Kazakhstan, and the Ukraine (Virta, 2006). 'Apparent' world consumption of asbestos was 2.11 million metric tons in 2003, with the Russian Federation, several former Russian states and countries in Asia being the predominant users (Virta, 2006). Consumption of asbestos in the USA (predominantly chrysotile) was 2230 metric tons in 2006, declining to 1730 metric tons in 2007 (Virta, 2008). Roofing products (includes coatings and compounds) accounted for over 80% of asbestos consumption in the USA (Virta, 2008; Virta, 2009). Asbestos products were banned in all the countries of the European Union, including Member States of eastern Europe, effective January 1, 2005 (EU, 1999).

1.4 Environmental occurrence

1.4.1 Natural occurrence

Asbestos minerals are widespread in the environment, and are found in many areas where the original rock mass has undergone metamorphism (ATSDR, 2001; USGS, 2001). Examples include large chrysotile deposits in the Ural Mountains in the Russian Federation, in the Appalachian Mountains in the USA, and in Canada (Virta, 2006). They may occur in large natural deposits or as contaminants in other minerals (e.g. tremolite asbestos may occur in deposits of chrysotile, vermiculite, and talc). The most commonly occurring form of asbestos is chrysotile, and its fibres are found as veins in serpentine rock formations. Asbestiform amphiboles occur in relatively low quantities throughout the earth's crust and their chemical composition reflects the environment in which they form (Virta, 2002). Although most commercial deposits typically contain 5–6% of asbestos, a few deposits, such

Table 1.2 Historical trend in asbestos use per capita and status of national ban

	Use of asbestos[a] (kg per capita/year)						
Country	**1950s**	**1960s**	**1970s**	**1980s**	**1990s**	**2000s**	**National ban[b]**
Asia							
Israel	3.13	2.87	1.23	0.78	0.44	0.02	No ban
Japan	0.56	2.02	2.92	2.66	1.81	0.46	2004
Others[c] (*n* = 39)	0.06	0.15	0.25	0.27	0.30	0.31	3/39
Eastern Europe and Southern Europe							
Croatia	0.39	1.13	2.56	2.36	0.95	0.65	No ban
Czech Republic	1.62	2.36	2.91	2.73	1.30	0.14	2005
Hungary	0.76	1.23	2.87	3.29	1.50	0.16	2005
Poland	0.36	1.24	2.36	2.09	1.05	0.01	1997
Romania	ND	ND	1.08	0.19	0.52	0.55	2007
Spain	0.32	1.37	2.23	1.26	0.80	0.18	2002
Others[c] (*n* = 15)	0.79	1.57	2.35	2.05	2.35	1.72	5/15
Northern Europe and Western Europe							
Austria	1.16	3.19	3.92	2.08	0.36	0.00	1990
Denmark	3.07	4.80	4.42	1.62	0.09	NA	1986
Finland	2.16	2.26	1.89	0.78	ND	0	1992
France	1.38	2.41	2.64	1.53	0.73	0.00	1996
Germany	1.84	2.60	4.44	2.43	0.10	0.00	1993
Iceland	0.21	2.62	1.70	0.02	0	0.00	1983
Lithuania	ND	ND	ND	ND	0.54	0.06	2005
Luxembourg	4.02	5.54	5.30	3.23	1.61	0.00	2002
Netherlands	1.29	1.70	1.82	0.72	0.21	0.00	1994
Norway	1.38	2.00	1.16	0.03	0	0.00	1984
Sweden	1.85	2.30	1.44	0.11	0.04	NA	1986
United Kingdom	2.62	2.90	2.27	0.87	0.18	0.00	1999
Others[c] (*n* = 5)	3.05	4.32	4.05	2.40	0.93	0.05	5/5

as the Coalinga chrysotile deposits in California, USA, are reported to contain 50% or more (USGS, 2001; Virta, 2006).

1.4.2 Air

Asbestos is not volatile; however, fibres can be emitted to the atmosphere from both natural and anthropogenic sources. The weathering of asbestos-bearing rocks is the primary natural source of atmospheric asbestos. No estimates of the amounts of asbestos released to the air from natural sources are available (ATSDR, 2001). Anthropogenic activities are the predominant source of atmospheric asbestos fibres. Major anthropogenic sources include: open-pit mining operations (particularly drilling and blasting); crushing, screening, and milling of the ore; manufacturing asbestos products; use of asbestos-containing materials (such as clutches and brakes on cars and trucks); transport and disposal of wastes containing asbestos; and, demolition of buildings constructed with asbestos-containing products, such as insulation, fireproofing, ceiling and floor tiles, roof shingles, drywall, and cement (ATSDR, 2001; NTP, 2005). Concentrations of asbestos vary on a site-by-site

Table 1.2 (continued)

	Use of asbestos[a] (kg per capita/year)						
Country	**1950s**	**1960s**	**1970s**	**1980s**	**1990s**	**2000s**	**National ban[b]**
Americas, excluding South America							
Canada	2.76	3.46	4.37	2.74	1.96	0.32	No ban
Cuba	ND	ND	ND	0.15	0.36	0.74	No ban
Mexico	0.28	0.57	0.97	0.77	0.39	0.26	No ban
USA	3.82	3.32	2.40	0.77	0.08	0.01	No ban
Others[c] (*n* = 12)	0.06	0.22	0.44	0.29	0.07	0.07	0/12
South America							
Argentina	ND	0.88	0.76	0.40	0.18	0.04	2001
Brazil	0.27	0.38	0.99	1.25	1.07	0.74	2001
Chile	0.07	0.92	0.56	0.64	0.55	0.03	2001
Ecuador	ND	ND	0.67	0.52	0.14	0.26	No ban
Uruguay	ND	0.74	0.75	0.54	0.47	0.08	2002
Others[c] (*n* = 6)	0.27	0.43	0.60	0.47	0.29	0.19	0/6
Oceania							
Australia	3.24	4.84	5.11	1.82	0.09	0.03	2003
New Zealand	2.05	2.56	2.90	1.00	ND	ND	No ban
Others[c] (*n* = 3)	ND	ND	ND	ND	ND	0.22	0/3

[a] Numbers corresponding to use of asbestos by country and region were calculated as annual use per capita averaged over the respective decade.
[b] Year first achieved or year planned to achieve ban. When shown as fraction, the numerator is the number of countries that achieved bans and the denominator is the number of other countries in the region.
[c] Data on asbestos use were available (but mortality data unavailable) for others in each region, in which case data were aggregated.
ND, no data available; NA, not applicable because of negative use data; 0.00 when the calculated data were < 0.005; 0 if there are no data after the year the ban was introduced.
From Nishikawa et al. (2008)

basis and, as a result, environmental emissions are not easily estimated (ATSDR, 2001).

1.4.3 Water

Asbestos can enter the aquatic environment from both natural and anthropogenic sources, and has been measured in both ground- and surface-water samples. Erosion of asbestos-bearing rock is the principal natural source. Anthropogenic sources include: erosion of waste piles containing asbestos, corrosion of asbestos-cement pipes, disintegration of asbestos-containing roofing materials, and, industrial wastewater run-off (ATSDR, 2001).

1.4.4 Soil

Asbestos can enter the soil and sediment through natural (e.g. weathering and erosion of asbestos-bearing rocks) and anthropogenic (e.g. disposal of asbestos-containing wastes in landfills) sources. The practice of disposing asbestos-containing materials in landfills was more common in the past, and is restricted in many countries by regulation or legislation (ATSDR, 2001).

1.4.5 Environmental releases

According to the US EPA Toxics Release Inventory, total releases of friable asbestos to the environment (includes air, water, and soil) in 1999 were 13.6 million pounds from 86 facilities

that reported producing, processing, or using asbestos (ATSDR, 2001). In 2009, total releases of 8.9 million pounds of friable asbestos were reported by 38 facilities (US EPA, 2010).

1.5 Human exposure

Inhalation and ingestion are the primary routes of exposure to asbestos. Dermal contact is not considered a primary source, although it may lead to secondary exposure to fibres, via ingestion or inhalation. The degree of penetration in the lungs is determined by the fibre diameter, with thin fibres having the greatest potential for deep lung deposition (NTP, 2005).

1.5.1 Exposure of the general population

Inhalation of asbestos fibres from outdoor air, and to a lesser degree in indoor air, is the primary route of exposure for the non-smoking general population. Exposure may also occur via ingestion of drinking-water, which has been contaminated with asbestos through erosion of natural deposits, erosion of asbestos-containing waste sites, corrosion of asbestos-containing cement pipes, or filtering through asbestos-containing filters. Families of asbestos-workers may be exposed via contact with fibres carried home on hair or on clothing.

In studies of asbestos concentrations in outdoor air, chrysotile is the predominant fibre detected. Low levels of asbestos have been measured in outdoor air in rural locations (typical concentration, 10 fibres/m^3 [f/m^3]). Typical concentrations are about 10-fold higher in urban locations and about 1000 times higher in close proximity to industrial sources of exposure (e.g. asbestos mine or factory, demolition site, or improperly protected asbestos-containing waste site) (ATSDR, 2001). Asbestos fibres (mainly chrysotile) were measured in air and in settled dust samples obtained in New York City following destruction of the World Trade Center on September 11, 2001 (Landrigan *et al.*, 2004).

In indoor air (e.g. in homes, schools, and other buildings), measured concentrations of asbestos are in the range of 30–6000 f/m^3. Measured concentrations vary depending on the application in which the asbestos was used (e.g. insulation versus ceiling or floor tiles), and on the condition of the asbestos-containing materials (i.e. good condition versus deteriorated and easily friable) (ATSDR, 2001).

1.5.2 Occupational exposure

Asbestos has been in widespread commercial use for over 100 years (USGS, 2001). Globally, each year, an estimated 125 million people are occupationally exposed to asbestos (WHO, 2006). Exposure by inhalation, and to a lesser extent ingestion, occurs in the mining and milling of asbestos (or other minerals contaminated with asbestos), the manufacturing or use of products containing asbestos, construction, automotive industry, the asbestos-abatement industry (including the transport and disposal of asbestos-containing wastes).

Estimates of the number of workers potentially exposed to asbestos in the USA have been reported by the National Institute of Occupational Safety and Health (NIOSH), by the Occupational Safety and Health Administration (OSHA), and the Mine Safety and Health Administration (MSHA). OSHA estimated in 1990 that about 568000 workers in production and services industries and 114000 in construction industries may have been exposed to asbestos in the workplace (OSHA, 1990). Based on mine employment data from 2002, NIOSH estimated that 44000 miners and other mine workers may have been exposed to asbestos during the mining of asbestos and some mineral commodities in which asbestos may have been a potential contaminant (NIOSH, 2002b). More recently, OSHA has estimated that 1.3 million employees in construction and

general industry face significant asbestos exposure on the job (OSHA, 2008). In addition to evidence from OSHA and MSHA that indicate a reduction in occupational exposures in the USA over the past several decades, other information compiled on workplace exposures to asbestos indicates that the nature of occupational exposures to asbestos has changed (Rice & Heineman, 2003). Once dominated by chronic exposures in manufacturing process such as textile mills, friction-product manufacturing, and cement-pipe fabrication, current occupational exposures to asbestos primarily occur during maintenance activities or remediation of buildings that contain asbestos.

In Europe, estimates of the number of workers exposed to asbestos have been developed by CAREX (CARcinogen EXposure). Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX database estimates that a total of 1.2 million workers were exposed to asbestos in 41 industries in the 15 Member States of the EU. Over 96% of these workers were employed in the following 15 industries: 'construction' (*n* = 574000), 'personal and household services' (*n* = 99000), 'other mining' (*n* = 85000), 'agriculture' (*n* = 81000), 'wholesale and retail trade and restaurants and hotels' (*n* = 70000), 'food manufacturing' (*n* = 45000), 'land transport' (*n* = 39000), 'manufacture of industrial chemicals' (*n* = 33000), 'fishing' (*n* = 25000), 'electricity, gas and steam' (*n* = 23000), 'water transport' (*n* = 21000), 'manufacture of other chemical products' (*n* = 19000), 'manufacture of transport equipment' (*n* = 17000), 'sanitary and similar services' (*n* = 16000), and 'manufacture of machinery, except electrical' (*n* = 12000). Despite the total ban of asbestos, about 1500 workers (mainly construction workers and auto mechanics) were reported as having exposure to asbestos on the Finnish Register of Workers Exposed to Carcinogens (ASA Register) in 2006 (Saalo *et al.*, 2006). In 2004, approximately 61000 workers performing demolition and reconstruction work in Germany were registered in the Central Registration Agency for Employees Exposed to Asbestos Dust (Hagemeyer *et al.*, 2006).

Exposure to asbestos in occupational settings is regulated in countries of the EU. According to the European Directive of the EC 2003/18, permissible limits are 0.1 [f/mL] for all types of asbestos, based on an 8-hour time-weighted average (8h-TWA) (EU, 2003). The same limit is in force in most Canadian provinces (Alberta, British Columbia, Manitoba, Ontario, Newfoundland and Labrador, Prince Edward Island, New Brunswick and Nova Scotia); New Zealand; Norway; and, the USA. Other countries have permissible limits of up to 2 fibres/cm^3 (ACGIH, 2007).

Since 1986, the annual geometric means of occupational exposure concentrations to asbestos reported in the OSHA database and the MSHA database have been consistently below the NIOSH recommended exposure limit (REL) of 0.1 f/mL for all major industry divisions in the USA. The number of occupational asbestos exposure samples that were measured and reported by OSHA decreased from an average of 890 per year during 1987–94 to 241 per year during 1995–99. The percentage exceeding the NIOSH REL decreased from 6.3% during 1987–1994 to 0.9% during 1995–99. During the same two periods, the number of exposures measured and reported in the MSHA database decreased from an average of 47 per year during 1987–94 to an average of 23 per year during 1995–99. The percentage exceeding the NIOSH REL decreased from 11.1% during 1987–94 to 2.6% during 1995–99 (NIOSH, 2002a).

Data from studies and reviews of occupational asbestos exposure published since the previous *IARC Monograph* (IARC, 1973) are summarized below.

(a) Studies of occupational exposure

In a mortality study of 328 employees of an asbestos-cement factory in Ontario, Canada, Finkelstein (1983) constructed an exposure model on the basis of available air sampling data, and calculated individual exposure histories to investigate exposure–response relationships for asbestos-associated malignancies. In retrospectively estimating exposure, the following assumptions were made: exposures did not change during 1962–70, exposures during 1955–61 were 30% higher than the later period, and exposures during 1948–54 were twice as high as during 1962–70. Exposure estimates for the years 1949, 1969, and 1979 were as follows: 40, 20, 0.2 f/mL for the willows operators; 16, 8, 0.5 f/mL for the forming machine operators; and, 8, 4, 0.3 f/mL for the lathe operators.

In an occupational hygiene survey of 24 Finnish workplaces, asbestos concentrations were measured during the different operations of brake maintenance of passenger cars, trucks and buses. During brake repair of trucks or buses, the estimated 8-hour time-weighted average exposure to asbestos was 0.1–0.2 [f/mL]. High levels of exposure (range, 0.3–125 [f/mL]; mean, 56 [f/mL]) were observed during brake maintenance if local exhaust ventilation was not used. Other operations in which the concentration exceeded 1 [f/mL] included cleaning of brakes with a brush, wet cloth or compressed air jet without local exhaust (Kauppinen & Korhonen, 1987).

Kimura (1987), in Japan, reported the following geometric mean concentrations: bag opening and mixing, 4.5–9.5 f/mL in 1970–75 and 0.03–1.6 f/mL in 1984–86; cement cutting and grinding, 2.5–3.5 f/mL in 1970–75 and 0.17–0.57 f/mL in 1984–86; spinning and grinding of friction products, 10.2–35.5 f/mL in 1970–75 and 0.24–5.5 f/mL in 1984–86.

Albin *et al.* (1990) examined total and cause-specific mortality among 1929 Swedish asbestos cement workers employed at a plant producing various products (e.g. sheets, shingles, ventilation pipes) from chrysotile and, to a lesser extent, crocidolite and amosite asbestos. Individual exposures were estimated using dust measurements available for the period 1956–77. Levels of exposure were estimated for the following operations: milling, mixing, machine line, sawing, and grinding. Asbestos concentrations ranged from 1.5–6.3 f/mL in 1956, to 0.3–5.0 f/mL in 1969, and to 0.9–1.7 f/mL in 1975. In all three time periods, the highest concentrations were observed in the milling and grinding operations.

The Health Effects Institute (1991) evaluated an operation and maintenance programme in a hospital on the basis of 394 air samples obtained during 106 on-site activities. The mean asbestos concentration was approximately 0.11 f/mL for personal samples, and approximately 0.012 f/mL for area samples. Eight-hour TWA concentrations showed that 99% of the personal samples were below 0.2 f/mL, and 95% below 0.1 f/mL.

Price *et al.* (1992) estimated the TWAs of asbestos exposures experienced by maintenance personnel on the basis of 1227 air samples collected to measure airborne asbestos levels in buildings with asbestos-containing materials. TWA exposures were 0.009 f/mL for telecommunication switch work, 0.037 f/mL for above-ceiling maintenance work, and 0.51 f/mL for work in utility spaces. Median concentrations were in the range of 0.01–0.02 f/mL.

Weiner *et al.* (1994) reported concentrations in a South African workshop in which chrysotile asbestos cement sheets were cut into components for insulation. The sheets were cut manually, sanded and subsequently assembled. Initial sampling showed personal sample mean concentrations of 1.9 f/mL for assembling, 5.7 f/mL for sweeping, 8.6 f/mL for drilling, and 27.5 f/mL for sanding. After improvements and clean-up of the work environment, the concentrations fell to 0.5–1.7 f/mL.

In a 1985 study, Higashi *et al.* (1994) collected personal and area samples at two manufacturing

and processing locations in five Japanese plants manufacturing asbestos-containing products (a roofing material plant; a plant making asbestos cement sheets; a friction-material plant; and two construction and roofing-material plants). Geometric average concentrations of 0.05–0.45 f/mL were measured in area samples, and 0.05–0.78 f/mL in personal samples.

To assess the contribution of occupational asbestos exposure to the occurrence of mesothelioma and lung cancer in Europe, Albin *et al.* (1999) reviewed and summarized the available information on asbestos consumption in Europe, the proportion of the population exposed and levels of exposure. Ranges of exposure were reported for the former Yugoslavia, Poland, and Latvia. In 1987, mean fibre concentrations in Serbia and Montenegro were 2–16 f/mL for textile manufacturing, 3–4 f/mL for friction materials production, and 1–4 f/mL for asbestos cement production. In Poland, exposure levels in 1994 were estimated to be much greater than 2 f/mL in the textile industry, approximately 2 f/mL in asbestos cement and friction-products manufacturing, and greater than 0.5 f/mL in downstream use. In the Latvian asbestos cement industry in 1994, ranges of fibre concentrations were 0.1–1.1 f/mL for the machine line, and 1.1–5.2 f/mL for the milling and mixing areas.

Since 1974, NIOSH has conducted a series of sampling surveys in the USA to gather information on exposure of brake mechanics to airborne asbestos during brake repair. These surveys indicated that the TWA asbestos concentrations (about 1–6 hours in duration) during brake servicing were in the range of 0.004–0.28 f/mL, and the mean TWA concentration, approxiamtely 0.05 f/mL (Paustenbach *et al.*, 2004).

Based on a review of the historical literature on asbestos exposure before 1972 and an analysis of more than 26000 measurements collected during 1972–90, Hagemeyer *et al.* (2006) observed a continual decrease in workplace levels of airborne asbestos from the 1950s to 1990 in Western Germany (FRG) and Eastern Germany (GDR). High concentrations of asbestos fibres were measured for some working processes in Western Germany (e.g. asbestos spraying (400 [f/mL]), removal of asbestos insulations in the ship repair industry (320 [f/mL]), removal of asbestos insulation (300 [f/mL]), and cutting corrugated asbestos sheets (60 [f/mL]), see Table 1.3.

In a study at a large petroleum refinery in Texas, USA, Williams *et al.* (2007a) estimated 8h-TWA asbestos exposures for 12 different occupations (insulators, pipefitters, boilermakers, masons, welders, sheet-metal workers, millwrights, electricians, carpenters, painters, laborers, and maintenance workers) from the 1940s to the 1985 onwards. Estimates were calculated using information on the historical use of asbestos, the potential for exposure due to daily work activities, occupational hygiene sampling data, historical information on task-specific exposures, and use of personal protective equipment. Exposures were estimated for 1940–50, 1951–65, 1966–71, 1972–75, 1976–85, and 1985 onwards. For these time periods, the 8h-TWA exposure (50th percentile) estimates for insulators were, respectively, 9 f/mL, 8 f/mL, 2 f/mL, 0.3 f/mL, 0.005 f/mL, and < 0.001 f/mL. For all other occupations, with the exception of labourers, estimated 8h-TWA exposure estimates were at least 50- to 100-fold less than that of insulators. Estimated 8h-TWA exposure estimates for labourers were approximately one-fifth to one-tenth of those of insulators.

Williams *et al.* (2007b) reviewed historical asbestos exposures (1940–2006) in various non-shipyard and shipyard settings for the following skilled occupations: insulators, pipefitters, boilermakers, masons, welders, sheet-metal workers, millwrights, electricians, carpenters, painters, labourers, maintenance workers, and abatement workers. For activities performed by insulators in various non-shipyard settings from the late 1960s and early 1970s, average task-specific and/or full-shift airborne fibre concentrations

Table 1.3 Examples of asbestos fibre concentrations in the air (f/cm^3) of different workplaces in Germany

Work area		1950–54[a]	1970–74	1980	1990
Textile industries	FRG	100	10	3.8	0.9
	GDR	100	12	6.2	2.2
Production of gaskets	FRG	60	6.6	4.7	0.7
	GDR	60	8.0	7.8	1.6
Production of cement	FRG	200	11	1.1	0.3
	GDR	200	13	1.9	0.7
Production of brake pads	FRG	150	9.1	1.4	0.7
	GDR	150	11	2.4	1.6
Insulation works	FRG	15	15	8.6	0.2
	GDR	18	18	14.0	0.5

[a] Data for the GDR before 1967 are extrapolated
FRG, Federal Republic of Germany; GDR, German Democratic Republic
From Hagemeyer et al. (2006)

ranged from about 2 to 10 f/mL. Average fibre concentrations in US shipyards were about 2-fold greater, and excessively high concentrations (attributed to the spraying of asbestos) were reported in some British Naval shipyards. The introduction of improved occupational hygiene practices resulted in a 2- to 5-fold reduction in average fibre concentrations for insulator tasks. The typical range of average fibre concentration for most other occupations was < 0.01–1 f/mL. Concentrations varied with task and time period, with higher concentrations observed for tasks involving the use of powered tools, the mixing or sanding of drywall cement, and the cleanup of asbestos insulation or lagging materials. It was not possible with the available data to determine whether the airborne fibres were serpentine or amphibole asbestos.

Madl *et al.* (2007) examined seven simulation studies and four work-site industrial hygiene studies to estimate the concentration of asbestos fibres to which workers may have historically been exposed while working with asbestos-containing gaskets and packing materials in specific industrial and maritime settings (e.g. refinery, chemical, ship/shipyard). These studies involved the collection of more than 300 air samples and evaluated specific activities, such as the removal and installation of gaskets and packings, flange cleaning, and gasket formation. In all but one of the studies, the short-term average exposures were less than 1 f/mL, and all of the long-term average exposures were less than 0.1 f/mL. Higher short-term average concentrations were observed during the use of powered tools versus hand-held manual tools during gasket formation (0.44 f/mL versus 0.1 f/mL, respectively). Peak concentrations of 0.14 f/mL and 0.40 f/mL were observed during 'gasket removal and flange face cleaning with hand tools' and 'packing removal and installation', respectively.

(b) Dietary exposure

The general population can be exposed to asbestos in drinking-water. Asbestos can enter potable water supplies through the erosion of natural deposits or the leaching from waste asbestos in landfills, from the deterioration of asbestos-containing cement pipes used to carry drinking-water or from the filtering of water supplies through asbestos-containing filters. In the USA, the concentration of asbestos in most drinking-water supplies is less than 1 f/mL, even in areas with asbestos deposits or with

asbestos cement water supply pipes. However, in some locations, the concentration in water may be extremely high, containing 10–300 million f/L (or even higher). The average person drinks about 2 litres of water per day (ATSDR, 2001). Risks of exposure to asbestos in drinking-water may be especially high for small children who drink seven times more water per day per kg of body weight than the average adult (National Academy of Sciences, 1993).

1.6 Talc containing asbestiform fibres

Talc particles are normally plate-like. These particles, when viewed on edge under the microscope in bulk samples or on air filters, may appear to be fibres, and have been misidentified as such. Talc may also form true mineral fibres that are asbestiform in habit. In some talc deposits, tremolite, anthophyllite, and actinolite may occur. Talc containing asbestiform fibres is a term that has been used inconsistently in the literature. In some contexts, it applies to talc containing asbestiform fibres of talc or talc intergrown on a nanoscale with other minerals, usually anthophyllite. In other contexts, the term asbestiform talc has erroneously been used for talc products that contain asbestos. Similarly, the term asbestiform talc has erroneously been used for talc products that contain elongated mineral fragments that are not asbestiform. These differences in the use of the same term must be considered when evaluating the literature on talc. For a more detailed evaluation of talc not containing asbestiform fibres, refer to the previous *IARC Monograph* (IARC, 2010).

1.6.1 Identification of the agent

Talc (CAS No. 14807-96-6) is a designation for both the mineral talc and for commercial products marketed as 'talc', which contain the mineral in proportions in the range of 35% to almost 100%. Commercial talc is classified as 'industrial talc' (refers to products containing minerals other than talc), 'cosmetic talc' (refers to products, such as talcum powder, which contain > 98% talc), and 'pharmaceutical talc' (refers to products containing > 99% talc) (Rohl *et al.*, 1976; Zazenski *et al.*, 1995). Synonyms for talc include: Agalite, French chalk, kerolite, snowgoose, soapstone, steatite, talcite, and talcum.

1.6.2 Chemical and physical properties of the agent

The molecular formula of talc is $Mg_3Si_4O_{10}(OH)_2$. It is a hydrated magnesium sheet silicate mineral, whose structure is composed of a layer of $MgO_4(OH)_2$ octahedra sandwiched between identical layers of SiO_4 tetrahedra. In nature, the composition of talc varies depending on whether or not the magnesium has been substituted with other cations, such as iron, nickel, chromium or manganese (Rohl *et al.*, 1976; IMA, 2005). Pure talc is translucent, appearing white when finely ground (Zazenski *et al.*, 1995). The colour of talc changes in the presence of substituted cations, ranging from pale-green to dark-green, brownish or greenish-grey. Talc has the following chemical and physical properties: melting point, 1500°C; hardness, 1 on the Moh's scale of mineral hardness; density, 2.58–2.83; and cleavage, (001) perfect (Roberts *et al.*, 1974). Talc is a very stable mineral, and is insoluble in water, weak acids and alkalis, is neither explosive nor flammable, and has very little chemical reactivity (IMA, 2005).

Talc's structure is crystalline. It can have a small, irregular plate structure (referred to as microcrystalline talc) or it can have large, well defined platelets (referred to as macrocrystalline talc). Its platyness and crystallinity determine the specific commercial applications for which it is suitable (Zazenski et al, 1995). Talc is formed by complex geological processes acting on pre-existing rock formations with diverse chemical composition (Rohl *et al.*, 1976). Many talc-bearing

rocks are formed from magnesia- and silica-rich ultramafic rocks. These rocks have a central core of serpentinite surrounded by successive shells of talc-abundant rock (e.g. talc carbonate and steatite). The serpentinite core is composed mostly of non-asbestiform serpentine minerals (lizardite and antigorite); however, small amounts of chrysotile asbestos may occur. (Zazenski *et al.*, 1995).

More detail on the chemical and physical properties of talc can be found in the previous *IARC Monograph* (IARC, 2010).

1.6.3 Use of the agent

Talc has several unique chemical and physical properties (such as platyness, softness, hydrophobicity, organophilicity, inertness) that make it desirable for a wide range of industrial and commercial applications (e.g. paint, polymers, paper, ceramics, animal feed, rubber, roofing, fertilizers, and cosmetics). In these products, talc acts as an anti-sticking and anti-caking agent, lubricant, carrier, thickener, absorbent, and strengthening and smoothing filler (IMA, 2005).

In 2000, the worldwide use pattern for talc was as follows: paper industry, 30%; ceramics manufacture, 28%; refractories, 11%; plastics, 6%; filler or pigment in paints, 5%; roofing applications, 5%; cement, 3%; cosmetics, 2%; and other miscellaneous uses, 10% (includes agriculture and food, art sculpture, asphalt filler, autobody filler, construction caulks, flooring, and joint compounds) (Roskill Information Services Ltd, 2003). According to a Mineral Commodity Summary published by the USGS in 2009, talc produced in the USA was used for ceramics, 31%; paper, 21%; paint, 19%; roofing, 8%; plastics, 5%; rubber, 4%; cosmetics, 2%; and other, 10% (Virta, 2009).

No information on the use of asbestiform talc in various industries (apart from mining and milling of talc from deposits containing asbestiform fibres) was identified by the Working Group. For a more detailed description of the uses of talc, refer to the previous *IARC Monograph* (IARC, 2010).

1.6.4 Environmental occurrence

(a) Natural occurrence

Primary talc deposits are found in almost every continent around the world. Talc is commonly formed by the hydrothermal alteration of magnesium- and iron-rich rocks (ultramafic rocks) and by low-grade thermal metamorphism of siliceous dolomites (Zazenski *et al.*, 1995). For more detailed information on the formation of commercially important talc deposits, refer to the previous *IARC Monograph* (IARC, 2010).

Talc deposits whose protoliths are ultramafic rocks (or mafic) are abundant in number but small in total production. They are found in discontinuous bodies in orogenic belts such as the Alps, the Appalachians, and the Himalayas; these types of talc deposits form during regional metamorphism accompanying orogenesis. They also occur in the USA (California, Arkansas, Texas), Germany, Norway, Canada (Ontario and Quebec), southern Spain, Finland, the Russian Federation (Shabry and Miassy), and Egypt. Chlorite and amphibole are usually associated with this type of talc deposit although they are commonly separated in space from the talc ore (Vermont). The amphiboles may or may not be asbestiform, depending on the local geological history (IARC, 2010).

Talc deposits formed from the alteration of magnesian carbonate and sandy carbonate such as dolomite and limestone are the most important in terms of world production. Two types are recognized:

- those derived from hydrothermal alteration of unmetamorphosed or minimally metamorphosed dolomite such as found in Australia (Mount Seabrook and Three Springs); USA (Wintersboro, Alabama; Yellowstone, Montana; Talc City, California; Metaline Falls, Washington;

and West Texas); the Republic of Korea; the People's Republic of China; India; the Russian Federation (Onot); and, northern Spain (Respina)

- those derived from hydrothermal alteration (including retrograde metamorphism) of regionally metamorphosed siliceous dolomites and other magnesium-rich rocks such as in the USA (Murphy Marble belt, North Carolina; Death Valley-Kingston Range, California; Gouverneur District, New York; Chatsworth, Georgia); Canada (Madoc); Italy (Chisone Valley); the Russian Federation (Krasnoyarsk); Germany (Wunsiedel); Austria (Leoben); Slovakia (Gemerska); Spain; France (Trimouns); and Brazil (Brumado) (IARC, 2010).

In a study to examine the amphibole asbestos content of commercial talc deposits in the USA, Van Gosen *et al.* (2004) found that the talc-forming environment (e.g. regional metamorphism, contact metamorphism, or hydrothermal processes) directly influenced the amphibole and amphibole-asbestos content of the talc deposit. Specifically, the study found that hydrothermal talcs consistently lack amphiboles as accessory minerals, but that contact metamorphic talcs show a strong tendency to contain amphiboles, and regional metamorphic talc bodies consistently contain amphiboles, which display a variety of compositions and habits (including asbestiform). Death Valley, California is an example of a contact metamorphic talc deposit that contains accessory amphibole-asbestos (namely talc-tremolite).

1.6.5 Human exposure

(a) Exposure of the general population

Consumer products (e.g. cosmetics, pharmaceuticals) are the primary sources of exposure to talc for the general population. Inhalation and dermal contact (i.e. through perineal application of talcum powders) are the primary routes of exposure. As talc is used as an anti-sticking agent in several food preparations (e.g. chewing gum), ingestion may also be a potential, albeit minor, route of exposure.

As late as 1973, some talc products sold in the USA contained detectable levels of chrysotile asbestos, tremolite, or anthophyllite (Rohl *et al.*, 1976), and it is possible that they remained on the market in some places in the world for some time after that (Jehan, 1984). Some of the tremolite and anthophyllite may have been asbestiform in habit (Van Gosen, 2006).

Blount (1991) examined pharmaceutical- and cosmetic-grade talcs for asbestiform amphibole content using a density-optical method. High-grade talc product samples (n = 15) were collected from deposits in Montana, Vermont, North Carolina, Alabama, and from outside the USA but available in the US market. Samples were uniformly low in amphibole content (with counts in the range of 0–341 particles/mg), and some samples appeared to be completely free of amphibole minerals. In samples containing amphibole minerals, cleavage-type and asbestos-type minerals were observed. Only one sample was found to contain an amphibole particle size distribution typical of asbestos.

More complete information on the levels of exposure experienced by the general population can be found in the previous *IARC Monograph* (IARC, 2010).

(b) Occupational exposure

Inhalation is the primary route of exposure to talc in occupational settings. Exposure by inhalation to talc dust occurs in the talc-producing industries (e.g. during mining, crushing, separating, bagging, and loading), and in the talc-using industries (e.g. rubber dusting and addition of talcs to ceramic clays and glazes). Because industrial talc is a mixture of various associated minerals, occupational exposure is to a mixture of mineral dusts (IARC, 1987b).

In general, data on numbers of workers occupationally exposed to talc are lacking. The National Occupation Exposure Survey (NOES), which was conducted by the US National Institute for Occupational Safety and Health (NIOSH) during 1981–83, estimated that 1.4 million workers, including approximately 350000 female workers, were potentially exposed to talc in the workplace (NIOSH, 1990). CAREX reports that approximately 28000 workers were exposed to talc containing asbestiform fibres in the workplace within the 15 countries that comprised the EU during 1990–93; however, some major industries producing or using talc were not included.

Many of the early measurements reported very high levels of talc dust exposures in mining and milling operations, often in the range of several mg/m^3, but there is evidence of decreasing exposures (IARC, 1987b; IARC, 2010). For example, before the adoption of technical preventive means in 1950, exposures in the talc operation in the Germanasca and Chisone Valley (Piedmont), Italy, were reported to be approximately 800 mppcf in the mines, and approximately 25 mppcf in the mills. Exposures in both areas were reduced to less than 10 mppcf after 1965 when improved occupational hygiene practices were implemented (Rubino *et al.*, 1976). Although the presence of asbestiform talc was often not reliably verified, it is likely that these levels have also decreased, in part due to mine closures and regulatory controls.

Oestenstad *et al.* (2002) developed a job–exposure matrix for respirable dust, covering all work areas in an industrial grade (tremolitic) talc mining and milling facility in upstate New York, USA. The facility started operating in 1948 with the opening of an underground mine (Mine 1) and a mill (Mill 1). An open pit mine (Mine 2) opened in 1974. Talc from the facility was used predominantly for manufacturing paint and ceramic tiles. The range of all respirable dust concentrations measured in the two baseline exposure surveys was 0.01–2.67 mg/m^3, with an arithmetic mean of 0.47 mg/m^3 and a geometric mean of 0.28 mg/m^3.

Only limited information is available about exposures in secondary industries in which talc is used or processed further. The previous *IARC Monograph* on talc (IARC, 2010) summarizes three historical surveys conducted in these kinds of industries. The IARC Working Group in 1987 noted, however, that even when measurements of respirable fibres were reported, no electron microscopic analysis was conducted to confirm the identity of the fibres. Recently, most industries using talc use non-asbestiform talc (IARC, 2010).

For a more complete description of studies in which occupational exposure to talc and talc-containing products has been reported, refer to the previous *IARC Monograph* (IARC, 2010).

2. Cancer in Humans

2.1 Introduction

The previous *IARC Monographs* were limited to the same six commercial forms of asbestos fibres (chrysotile, actinolite, amosite, anthophyllite crocidolite and tremolite) that are subject of this current evaluation. In the previous *IARC Monograph* (IARC, 1977), the epidemiological evidence showed a high incidence of lung cancer among workers exposed to chrysotile, amosite, anthophyllite, and with mixed fibres containing crocidolite, and tremolite. Pleural and peritoneal mesotheliomas were reported to be associated with occupational exposures to crocidolite, amosite, and chrysotile. Gastrointestinal tract cancers were reported to have been demonstrated in groups occupationally exposed to amosite, chrysotile or mixed fibres containing chrysotile. An excess of cancer of the larynx in occupationally exposed individuals was also noted. Finally the *Monograph* points out that mesothelioma may occur among individuals

living in neighbourhoods of asbestos factories and crocidolite mines, and in persons living with asbestos workers.

Extensive epidemiological research on asbestos has been conducted since then. The associations between asbestos exposure, lung cancer, and mesothelioma have been well established in numerous epidemiological investigations. The epidemiological evidence for other cancer sites is less extensive than it is for lung cancer and mesothelioma, but is still considerable for some. In reviewing these studies, there are some common limitations that need to be borne in mind, which may explain the heterogeneity of the findings from the studies such as:

- The types, fibre sizes and levels of asbestos exposure differed from industry to industry and over time. Most of the heaviest exposures probably occurred in the first two-thirds of the twentieth century in asbestos mining and milling, insulation work, shipyard work, construction, and asbestos textile manufacture. Workers in different industries, eras, and geographic locales were exposed to different types of asbestos fibres, and to fibres of greatly varying dimensions.
- There were differences in how the studies handle the issue of latency or in other words time since first occupational exposure to asbestos. Some studies, especially earlier investigations, accumulated person–years from first exposure, a procedure that may dilute observed risk by including many years of low risk. Others have only accumulated person–years after a certain period of time after first exposure, usually 20 years. Also different studies followed their populations for very different periods of time since first occupational exposure to asbestos.
- The most pervasive problem in interpreting studies was the wide variation among studies in the approaches taken for exposure assessment. Some studies made no attempt to assess exposure beyond documenting employment of study participants in a trade or industry with potential for occupational exposure to asbestos. Other studies used surrogate indices of exposure such as duration of employment or self-reported intensity of exposure, or stratified subjects' exposure by job title. Some used the skills and knowledge of industrial hygienists, obtained direct measurements of asbestos dust levels in air, and developed job–exposure matrices and cumulative exposure indices. Even these analyses are limited by the fact that earlier studies used gravimetric measures of dust exposure, while later used fibre-counting methods based on phase contrast microscopy (PCM). Factors that were used to convert between gravimetric and PCM based measurements are generally unreliable unless they are based on side by side measurements taken in specific industrial operations. Differences in fibre size distributions and fibre type can only be detected using electron microscopy, which has been done in only a very few studies.
- Misclassification of disease was a serious problem for several of the cancer sites. This is particularly true for mesothelioma, which did not have diagnostic category in the ICD system until the 10th review was initiated in 1999.

There were also issues regarding the potential for misclassification of mesotheliomas as colon or ovarian cancers.

For talc that contains asbestiform fibres, previous Working Groups assessed studies on talc described as containing asbestiform tremolite and anthophyllite (IARC, 1987a, b). These fibres fit the definition of asbestos, and therefore a separate review of talc containing asbestiform fibres was not undertaken by this Working Group. The

reader is invited to consult the General Remarks in this volume for further details. For a review of Talc, refer to the previous *IARC Monograph* (IARC, 2010).

2.2 Cancer of the lung

2.2.1 Occupational exposure

Signs that cancer of the lung could be induced by exposure to asbestos was first raised by reports of lung cancer cases that occurred among workers with asbestosis (Gloyne, 1935; Lynch & Smith, 1935). The first cohort study that demonstrated an excess of lung cancer among asbestos exposed workers was a study of textile workers (Doll, 1955). In this study, 11 cases of lung cancer versus 0.8 expected ($P < 0.00001$) were reported based on national mortality rates. Since 1955, an association between lung cancer and occupational exposure to asbestos has been demonstrated in numerous cohort and case–control studies that are summarized in Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.1.pdf, Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.2.pdf, and Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.3.pdf.

Although a causal association between asbestos exposure and lung cancer is generally well recognized, there are still substantial controversies on how the risk might vary by exposure to different fibre types and sizes, and whether there is a risk at low levels of exposure (i.e. environmental exposures). Particularly controversial is the question of whether chrysotile asbestos is less potent for the induction of lung cancer than the amphibole forms of asbestos (e.g. crocidolite, amosite and tremolite), which has sometimes been referred to as the "amphibole hypothesis" (Cullen, 1996; Stayner *et al.*, 1996; McDonald, 1998). This argument is based on the observation from experimental studies that chrysotile asbestos is less biopersistent (i.e. has a shorter half life) in the lung than the amphiboles. Pathological studies of tissue using electron microscopy and energy dispersive analysis of X-rays (EDAX) have been used to measure the amounts of different asbestos fibre types in the lung. Case studies of Canadian chrysotile asbestos workers using these methods have shown an unexpectedly high proportion of amphibole (primarily tremolite) fibres, considering the relatively low percentage of amphibole fibres in commercial chrysotile asbestos (Pooley, 1976; Rowlands *et al.*, 1982; Addison & Davies, 1990). [The Working Group noted that the lower biopersistence of chrysotile in the lung does not necessarily imply that it would be less potent than amphiboles for lung cancer.]

Several meta-analyses have been conducted in which the relative potency of different fibre types and other fibre characteristics have been considered in relation to lung cancer. Lash *et al.* (1997) conducted a meta-analysis based on the findings from 15 cohort studies with quantitative information on the relationship between asbestos exposure and lung cancer risk. The slopes of the lung cancer exposure–response relationship from these studies were analysed using fixed and random effects models. Substantial heterogeneity in the slopes for lung cancer from these studies was found in their analysis. The heterogeneity was largely explained by industry category, dose measurements, tobacco habits, and standardization procedures. There was no evidence in this meta-analysis that differences in fibre type explained the heterogeneity of the slope.

Hodgson & Darnton (2000) performed a meta-analysis based on 17 cohort studies with information on the average level of asbestos exposure for the cohort as a whole or for subgroups in the study. The percentage excess lung cancer risk from each study or subgroup was divided by its average exposure level to derive a slope (RL) for the analysis. Substantial heterogeneity in the

findings for lung cancer was also found in this analysis particularly for the chrysotile cohorts. The heterogeneity in the findings for the chrysotile cohorts was largely attributable to differences in the findings from the studies of chrysotile miners and millers in Quebec (McDonald *et al.*, 1983), and asbestos textile workers in South Carolina (Dement & Brown, 1994; Hein *et al.*, 2007), which differed by nearly 100-fold. No explanation has been found for these extreme differences although several possible explanations have been investigated. Co-exposure to mineral oils in the South Carolina textile plant was proposed as a possible explanation. A nested case–control conducted with the South Carolina cohort failed to provide evidence to support the hypothesis that mineral exposure was associated with an increased risk of lung cancer in this study population (Dement & Brown, 1994). Differences in fibre size distributions have also been considered to be a potential explanation. The asbestos textile industry workers may have used a higher grade of asbestos resulting in exposures to a greater percentage of long fibres than what was experienced by miners and millers in Quebec. A larger percentage of long fibres was found in a recent reanalysis of samples from the South Carolina cohort using transmission electron microscopy (TEM) (Dement *et al.*, 2008) than what was previously reported in TEM analyses of samples from the Quebec mines and mills (Gibbs & Hwang, 1975, 1980). Based on their analysis, Hodgson & Darnton (2000) concluded that the ratio between lung cancer risk for chrysotile and the amphiboles was somewhere between 1:10 and 1:50. However, in their analyses (where they excluded the study of Quebec miners rather than the South Carolina cohort), there was only a 2-fold difference in findings for lung cancer risk between the chrysotile (RL = 2.3) and amphibole cohorts (RL = 4.2). [The Working Group noted that there is no justification for exclusion of the South Carolina cohort because it is one of the highest quality studies in terms of the exposure information used in this study.]

Berman & Crump (2008a) published a meta-analysis that included data from 15 asbestos cohort studies. Lung cancer risk potency factors (Kis = [RR-1]/cumulative exposure) were derived in their analyses that were specific for both fibre type (chrysotile versus amphiboles) and fibre size (length and width). Fibre size information was only available for one of the cohort studies, and for the other studies it was obtained from studies that were conducted in similar industrial settings. As with the previous analyses, substantial variation was found in the findings from these studies with results for lung cancer varying by two orders of magnitude, although no formal statistical tests of heterogeneity were performed. The hypothesis that chrysotile is equipotent as the amphiboles for lung cancer was not rejected for fibres of all widths ($P = 0.07$) or for thick (width > 0.2 µm) fibres ($P = 0.16$). For thin fibres (width < 0.2 µm), there was significant ($P = 0.002$) evidence that chrysotile fibres were less potent than amphiboles. Sensitivity analyses were also conducted in which the South Carolina or Quebec miners and millers cohorts were dropped from the analysis using fibres of all widths. Dropping the South Carolina cohort resulted in a highly significant ($P = 0.005$) result that potency was greater for amphiboles than for chrysotile. Dropping the Quebec cohort resulted in there being no significant ($P = 0.55$) evidence of a difference in potency between the fibre types. [The Working Group noted that both the Hodgson & Darnton and Berman & Crump analyses reveal a large degree of heterogeneity in the study findings for lung cancer, and that findings are highly sensitive to the inclusion or exclusion of the studies from South Carolina or Quebec. The reasons for the heterogeneity are unknown, and until they are explained it is not possible to draw any firm conclusions concerning the relative potency of chrysotile and amphibole asbestos fibres from these analyses.]

Based on findings from experimental studies, it is suspected that long and thin fibres are likely to be more potent than short and thick fibres in the induction of lung cancer in humans. Unfortunately until recently, all of the epidemiological studies that have been conducted used methods for exposure assessment that did not include a determination of fibre size, and thus this issue could not be directly addressed with these studies. As described above, the meta-analysis conducted by Berman & Crump (2008a) considered the effect of fibre size on lung cancer risk by using data from other studies conducted in similar circumstances as the cohort studies. Their analysis did not reveal strong evidence that lung cancer potency was dependent on fibre size. There was weak evidence that long fibres (length > 10 μm) were more potent than short fibres (5 μm < length < 10 μm) in models using all widths (P = 0.07). The lack of size-specific data from the studies was a major limitation of this study with regard to estimating size-specific risk estimates. Stayner *et al.* (2008) published findings from an analysis of the South Carolina asbestos textile cohort in which fibre size specific estimates of lung cancer mortality was evaluated using information from a reanalysis of archived air samples using TEM (Dement *et al.*, 2008). Long fibres (> 10 μm) and thin fibres (< 0.25 μm) were found to be the strongest predictors of lung cancer mortality in this study.

Another study not part of the prior meta-analyses provides relevant information regarding the question of the relative lung cancer potency of the fibre types. Loomis *et al.* (2009) carried out a retrospective cohort mortality study of textile workers from four plants in North Carolina that had never been studied before. Workers in this cohort were primarily exposed to chrysotile asbestos that was imported from Quebec. A small amount of amosite was used in an operation in one of the plants. Overall, an excess of lung cancer was observed in this study (SMR, 1.96; 95%CI: 1.73–2.20), which was very similar in magnitude to that reported in the South Carolina cohort study of textile workers (Hein *et al.*, 2007). However, the slope for the exposure–response between asbestos exposure and lung cancer was considerably lower than that reported in the South Carolina cohort study. The reasons for these differences in the exposure–response relationships are unknown, but one possible reason may be that quality of the exposure information was superior in the South Carolina study, and that the difference could be explained by an attenuation of the slope due to exposure misclassification in Loomis *et al.* (2009).

2.2.2 Environmental exposures

Evidence of an association in women between lung cancer and environmental exposures in New Caledonia to field dust containing tremolite and the use of a whitewash ("po") containing tremolite has been reported (Luce *et al.*, 2000). A positive association with heavy residential exposure to asbestos was observed in a lung cancer case–control study the Northern Province of South Africa, which is a crocidolite and amosite mining area (Mzileni *et al.*, 1999). The association was strongest among women who resided in heavily exposed areas (odds ratio [OR], 5.4; 95%CI: 1.3–22.5; Ptrend = 0.02). A study of lung cancer mortality among women in two chrysotile mining regions of Quebec did not result in an increase in lung cancer (SMR, 0.99; 95%CI: 0.78–1.25) relative to women from 60 other areas of Canada (Camus *et al.*, 1998).

2.2.3 Non-commercial asbestiform amphibole fibres

There is emerging epidemiological evidence that non-commercial amphibole fibres that are asbestiform have carcinogenic potential. These fibres are not technically "asbestos," and they were never commercially marketed. However, the Working Group felt it was important to

discuss the recent evidence concerning these fibres because of their similarity to asbestos, and because of public concerns regarding this issue.

Several studies have described adverse health associations with the amphibole fibres that contaminated vermiculite mined in Libby, Montana, USA. These fibres were originally characterized as from the tremolite-actinolite series (IARC, 1987a), however, they have been more recently described by the US Geological Society as approximately 84% winchite, 11% richterite, and 6% tremolite (Meeker *et al.*, 2003). Sullivan (2007) reported standardized mortality ratios (SMRs), using cause of death data and expected mortality for the underlying cause of death based on national age-, race-, and sex-specific rates. Using a 15-year exposure lag, there were increased SMRs for all cancer (SMR, 1.4; 95%CI: 1.2–1.6; $n = 202$), and lung cancer (SMR, 1.7; 95%CI: 1.4–2.1; $n = 89$). Increasing risks were observed across categories of cumulative exposure; the SMR estimates were 1.5, 1.6, 1.8, and 1.9 in the 1–4.49, 4.5–22.9, 23.0–99.0, and ≥ 100 f/mL–years exposure categories, respectively. Results from other studies (Amandus *et al.*, 1987; McDonald *et al.*, 2004) of analyses using a continuous measure of exposure also resulted in statistically significant relationships with lung cancer mortality risk. For example, in the updated analysis by McDonald *et al.* (2004), the estimated linear increase in relative risk of respiratory cancer risk per 100 f/mL–years cumulative exposure was 0.36 (95%CI: 0.03–1.2; $P = 0.02$).

2.3 Mesothelioma

Pleural and peritoneal mesotheliomas are very rare malignancies that occur in the mesothelial cells that line these cavities. The first report of a possible association between asbestos exposure and mesothelioma was by Wagner *et al.* (1960) who described an outbreak of mesothelioma in a crocidolite mining region of South Africa. The majority of the cases reported had worked in the mines (23/33) but some of the cases had also occurred among individuals with no history of occupational exposures (10/33). Since then, an excess of mesothelioma has been observed in a large number of cohort and case–control studies (summarized in online Tables 2.2, 2.3 and Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.4.pdf) in a variety of different industries using and producing asbestos. Although the causal association between mesothelioma and asbestos has been well established, several important issues remain to be resolved that are discussed below.

2.3.1 Fibre type

Although all forms of asbestos can cause mesothelioma, there is considerable evidence that the potency for the induction of mesothelioma varies by fibre type, and in particular that chrysotile asbestos is less potent than amphibole forms of asbestos. An excess of mesothelioma has been reported in cohort studies of chrysotile exposed miners and millers in Quebec (Liddell *et al.*, 1997), and in South Carolina asbestos textile workers who were predominantly exposed to chrysotile asbestos imported from Quebec (Hein *et al.*, 2007). However, the fact that the chrysotile asbestos mined in Quebec is contaminated with a small percentage (< 1.0%) of amphibole (tremolite) asbestos has complicated the interpretation of these findings. McDonald *et al.* (1997) found in a nested case–control study for mesothelioma in the Thetford mines of Quebec that an association with asbestos exposure was evident in mines from a region with higher concentrations of tremolite, and not in another region with lower concentrations of tremolite. Bégin *et al.* (1992) noted that although tremolite levels may be 7.5 times higher in Thetford than in Asbestos, the incidence of mesothelioma in these two Quebec mining towns was proportional to the size of their workforce. This suggests that

the tremolitic content of the ores may not be a determinant of mesothelioma risk in Quebec. Separate analyses for workers at the Thetford and Asbestos mines and mills did not demonstrate a different exposure–response relationship for asbestos and mesothelioma in the two mining areas (McDonald & McDonald, 1995).

In a mesothelioma case–control study in South Africa, an association was reported with exposures to crocidolite and amosite asbestos, but no cases were found to have been exclusively exposed to chrysotile asbestos (Rees *et al.*, 1999). One possible explanation for these negative findings for chrysotile is that South African chrysotile asbestos may contain relatively little tremolite (Rees *et al.*, 1992). Another possible explanation is that chrysotile mining began later, and production levels were lower than in the crocidolite and amosite mines of South Africa. Cases of mesothelioma have been reported among asbestos miners in Zimbabwe, which has been reported to be uncontaminated with tremolite asbestos (Cullen & Baloyi, 1991). Excess mesothelioma mortality (standardized incidence ratio [SIR], 4.0, 95%CI: 1.5–8.7) was reported in miners and millers from a chrysotile mine in Balangero, Italy (Mirabelli *et al.*, 2008), reportedly free of amphibole contamination (Piolatto *et al.*, 1990).

An evaluation of the relative potency of the different fibre types of asbestos has been considered in the meta-analyses that were previously described (see prior section on lung cancer) by Hodgson & Darnton (2000) and Berman & Crump (2008a, b). Hodgson & Darnton (2000) used the percentage of mesothelioma deaths of all deaths expected (at an age of first exposure of 30) per unit of cumulative exposure (Rm) as the measure for their analysis. They computed separate estimates of Rm for crocidolite, amosite and chrysotile asbestos. Based on their analyses, they estimated that the ratio of the potency for mesothelioma (pleural and peritoneal combined) was 1:100:500 for chrysotile, amosite, and crocidolite respectively.

The meta-analysis conducted by Berman & Crump (2008a) was based on the analysis of the slopes (Km) that were estimated using an approach that assumes that the mortality rate from mesothelioma increases linearly with the intensity of exposure, and for a given intensity, increases indefinitely after exposure ceases, approximately as the square of time since first exposure (lagged 10 years). This model was tested with the raw data from several studies, and found to provide a good fit to the data (Berman & Crump, 2008b). Regression models were fitted to the study Km values that included information from surrogate studies to estimate fibre type (chrysotile versus amphiboles) and fibre length (short versus long) specific potency slopes (Berman & Crump, 2008a). Alternative models were fitted with exposure metrics based on different fibre widths. The hypothesis that chrysotile and amphibole forms of asbestos are equipotent was strongly rejected, and the hypothesis that potency for chrysotile asbestos was 0 could not be rejected based on their models ($P < 0.001$ and $P = 0.29$, respectively, for all-widths model). The best estimates for the relative potency of chrysotile ranged from zero to about 1/200th that of amphibole asbestos (depending on the width of the exposure metric used in the model). [The Working Group noted that there is a high degree of uncertainty concerning the accuracy of the relative potency estimates derived from the Hodgson & Darnton and Berman & Crump analyses because of the severe potential for exposure misclassification in these studies.]

Two newer studies, not part of the prior meta-analyses, provide important information regarding the question of the relative potency of the fibre types. The first is a study of a cohort of textile workers in North Carolina not previously examined (Loomis *et al.*, 2009). Workers in this cohort were primarily exposed to chrysotile asbestos imported from Quebec. A relatively large excess of both mesothelioma [SMR, 10.92; 95%CI: 2.98–27.96] and pleural cancer [SMR,

12.43; 95%CI: 3.39–31.83]. The pleural and mesothelioma deaths combined comprised 0.3% of all deaths. This percentage was nearly identical to the estimate developed for the chrysotile cohorts in a review article by Stayner *et al.* (1996). Based on the approach that Hodgson & Darnton used in their meta-analysis, the authors estimated that the percentage of deaths per unit of fibre exposure was 0.0058% per f–y/mL (0.0098% per f–y/mL for workers followed ≥ 20 years). This estimate was considerably higher than the estimate developed by Hodgson & Darnton of 0.0010% per f–yr/mL for cohorts exposed to chrysotile.

The other study investigated mesothelioma among chrysotile miners and millers, and resident communities in Balangero, Italy. The chrysotile mined at Balangero was reported to be free of tremolite and other amphiboles. The ore contains trace amounts of another fibre called blangeroite, which is not an amphibole (Turci *et al.*, 2009). A previous cohort of the miners and millers in Balangero with follow up to 1987 identified only two deaths from mesothelioma (Piolatto *et al.*, 1990). Cases of mesothelioma were identified from a local mesothelioma registry comprises people who had been mine employees; employees of subcontractors or other firms transporting or refining Balangero asbestos, asbestos ore; residents of the area who were exposed from air pollution, living with a mine employee or from mine tailings from Balangero. Six cases of mesothelioma were identified among blue-collar miners, and an estimated 1.5 deaths (SIR, 4.00; 95%CI: 1.47–8.71) would be expected based on a previous cohort study (Piolatto *et al.*, 1990), and conservative assumptions about the cohort. Additional cases of mesothelioma were identified among white-collar miners (three cases), workers in the mine hired by subcontractors (five cases), and from non-occupational exposures or exposure to re-used tailings (ten cases). Expected numbers of mesothelioma cases could not be derived for these groups because they were not part of the original cohort definition. The findings from this investigation indicate that the previous risk of mesothelioma for the Balangero cohort were seriously underestimated.

2.3.2 Fibre size

Based on a review of toxicological and human studies, Lippmann (1990) suggested that fibres shorter than 0.1 µm and longer than 5 µm are related to mesothelioma in humans. The Berman & Crump meta-analyses provided weak evidence that fibre length is a determinant of the potency of asbestos. The test of the hypothesis that long fibres (length ≥ 10 µm) and short fibres (5 < length < 10 µm) are equipotent was nearly rejected in some models (e.g. $P = 0.09$ for all widths). Thus, their findings provide weak support that long fibres may be more potent than short fibres for mesothelioma. There was little evidence in their analyses that thin fibres (width < 0.4 or < 0.2 µm) were stronger predictors of mesothelioma potency than all fibre widths combined. A major limitation of their analysis was that it relied on surrogate data to estimate the fibre-size distributions for the studies used in the meta-analysis.

2.3.3 Pleural versus peritoneal tumours

The ratio of pleural to peritoneal mesotheliomas has varied considerably in different epidemiological studies of asbestos-exposed cohorts. In the cohort studies included in the meta-analysis conducted by Hodgson & Darnton (2000), the percentage of mesotheliomas that were peritoneal varied from 0 to over 50%. Hodgson & Darnton reported that peritoneal mesotheliomas increased with the square of cumulative exposure to asbestos (i.e. a supralinear relationship); whereas pleural mesotheliomas increased less than linearly with cumulative exposure to asbestos. This implies that the number of peritoneal mesotheliomas would dramatically increase relative to the number of pleural mesotheliomas at high asbestos exposure levels. Welch *et al.*

(2005) found a strong association (OR, 5.0; 95%CI: 1.2–21.5) between asbestos exposure and peritoneal cancer in a population-based case–control study. This study included a large percentage of men with what were judged to be low exposures to asbestos.

2.3.4 Environmental exposures

An excess of mesothelioma has been observed in several studies of communities with environmental exposure to asbestos. A large excess of mesothelioma was reported in a study of people living in villages in Turkey exposed to erionite used to whitewash their homes (Baris *et al.*, 1987). An excess in mesothelioma was reported among people living near crocidolite mining regions in South Africa and Western Australia (Wagner & Pooley, 1986), among people residing in areas of tremolite contamination in Cyprus (McConnochie *et al.*, 1987) and New Caledonia (Luce *et al.*, 2000), and with non-occupational exposures in Europe (Magnani *et al.*, 2000), Italy (Magnani *et al.*, 2001), and California (Pan *et al.*, 2005).

Mesothelioma has also been reported to occur among household members of families of asbestos workers (Anderson *et al.*, 1976; Ferrante *et al.*, 2007).

2.3.5 Non-commercial asbestiform fibres

Several studies have described adverse health associations with the amphibole fibres that contaminated vermiculite mined in Libby, Montana, USA. These fibres were originally characterized as from the tremolite-actinolite series (IARC, 1987a); however, they were subsequently described by the US Geological Society as being composed of approximately 84% winchite, 11% richterite, and 6% tremolite (Meeker *et al.*, 2003). Sullivan (2007) reported SMRs, using cause of death data and expected mortality for the underlying cause of death based on national age-, race-, and sex-specific rates. Using a 15-year exposure lag, there were increased SMRs, mesothelioma defined by ICD-10 for deaths after 1999 (SMR, 14.1; 95%CI: 1.8–54.4; $n = 2$) and pleural cancer (SMR, 23.3; 95%CI: 6.3–59.5; $n = 4$). The only exposure–response modelling of mesothelioma was presented in the paper by McDonald *et al.*, based on 12 mesothelioma cases (McDonald *et al.*, 2004). Using Poisson regression, the mesothelioma mortality rate across increasing categories of exposure was compared with the rate in the lowest exposure category. For the cumulative exposure metric, the relative risk estimates were 1.0 (referent), 3.72, 3.42, and 3.68, based on 1, 4, 3, and 4, cases, respectively. The mean exposure level in these four quartiles was 8.6, 16.7, 53.2, and 393.8 f/mL–yr, respectively. It should be noted that the referent group was also at excess risk of dying from mesothelioma, i.e. there were 1–3 cases of mesothelioma observed in the referent group, which may have attenuated the observed effects.

A high incidence of mesothelioma was reported among residents of Biancavilla, Italy, a city in eastern Sicily (SMR, 7.21; 95%CI: 3.59–13.00). Reviewing of the work histories of the cases did not indicate an occupational explanation for these exposures, and thus environmental explanations for the mesothelioma excess were sought. Environmental studies have indicated that these mesotheliomas are most likely due to exposures to fluoro-edenite which is a newly recognized fibre that is very similar in morphology and composition to the tremolite-actinolite series (Comba *et al.*, 2003; Bruno *et al.*, 2006; Putzu *et al.*, 2006).

2.4 Other cancer sites

Beyond lung cancer and mesothelioma, the body of literature examining associations between asbestos and other cancers is more sparse. This reflects the fact that lung cancer and mesothelioma have been the principal areas of research

until relatively recently, and other cancers were often not considered in detail in published reports. Clinical and epidemiological studies that span the past five decades suggest, however, that asbestos may be associated with other cancers in addition to lung cancer and mesothelioma. To examine these associations in detail, the US IOM (2006) published a report evaluating the evidence relevant to causation of cancer of the pharynx, larynx, oesophagus, stomach, colon and rectum by asbestos. The present analysis draws on the IOM analysis and presents the most significant positive and negative studies for each anatomical site, with an emphasis on studies that presented data on dose–response as well as on published meta-analyses. Additionally, the present analysis examines the association between asbestos exposure and ovarian cancer, an association that was not examined by the IOM.

2.4.1 Cancer of the pharynx

See Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.5.pdf.

(a) Cohort Studies

The Working Group examined 16 cohort studies of asbestos and cancer of the pharynx. Some of these studies examined all cancers of the lips, oral cavity, and pharynx. Others restricted their examination to the pharynx itself. Two studies examined only cancers of the hypopharynx. The main findings are summarized in the following paragraphs.

Selikoff & Seidman (1991) observed an SMR for cancer of the oropharynx of 2.18 (95%CI: 1.62–2.91) among a cohort of 17800 male asbestos insulation workers across the USA and Canada. This is the cohort study with the largest number of deaths from pharyngeal cancer, a total of 48 deaths.

Piolatto *et al.* (1990) observed an SMR for cancer of the oropharynx of 2.31 (95%CI: 0.85–5.02; based on six deaths) in a cohort of 1058 asbestos miners in northern Italy exposed to chrysotile asbestos. No association was seen in this cohort between duration of occupational exposure to asbestos and risk of cancer of the pharynx.

Reid *et al.* (2004) observed an SMR for cancer of the pharynx of 1.88 (95%CI: 1.15–3.07; based on 16 deaths) in a cohort of 5685 crocidolite asbestos miners and millers in Western Australia.

Sluis-Cremer *et al.* (1992) observed an SMR for cancer of the lip, oral cavity and pharynx of 2.14 (95%CI: 1.03–3.94; based on 10 deaths) in a cohort of 7317 male asbestos miners in South Africa, some exposed to crocidolite and others to amosite. Cancer of the pharynx was defined in this population as cancer of the lip, oral cavity or pharynx. There was no excess mortality for cancer of the pharynx in the subcohort of amosite asbestos miners (SMR, 0.42; 95%CI: 0.00–1.97), but in the subcohort of crocidolite asbestos miners, the SMR for cancer of the pharynx was 2.94 (95%CI: 1.16–6.18).

Pira *et al.* (2005) observed an SMR for cancer fo the pharynx of 2.26 (95%CI: 0.90–4.65; based on seven deaths) in a cohort of 1996 workers in the asbestos textiles industry in Italy.

Other cohort studies of populations occupationally exposed to asbestos in a range of industries contained only small numbers of deaths from cancer of the pharynx (most < 10 deaths), were generally non-positive in their findings, and reported little evidence for dose–response relationships.

(b) Case–control studies

Case–control studies examining the association between asbestos exposure and cancer of the pharynx have two advantages over cohort studies:

1. they are able to collect more cases of this relatively uncommon malignancy; and
2. they are able to adjust for alcohol and tobacco consumption, the two most common causes

of cancer of the pharynx in developed and developing countries.

The present review included six case–control studies. Four of them adjusted for alcohol and tobacco consumption. The main findings are summarized in the following paragraphs.

Marchand *et al.* (2000) carried out a hospital-based, case–control study of 206 cases of cancer of the hypopharynx and 305 controls in France, and found a relative risk of 1.80 (95%CI: 1.08–2.99) in the 161 of their cases ever exposed to asbestos, adjusted for exposure to tobacco and alcohol.

Berrino *et al.* (2003) conducted a multicentre, case–control study of cancer of the hypopharynx in Europe, and found an odds ratio (OR) for "probable" exposure to asbestos of 1.8 (95%CI: 0.6–5.0). This study was restricted to analyses of cancers of the hypopharynx. For cases with "possible" exposure to asbestos, the odds ratio was 1.80 (95%CI: 0.90–3.90). These odds ratios were adjusted for exposure to tobacco and alcohol.

Zheng *et al.* (1992) conducted a population-based, case–control study of cancer of the pharynx in Shanghai, the People's Republic of China, with 204 incident cancer cases and 414 controls. The relative risk for asbestos exposure was 1.81 (95%CI: 0.91–3.60). Cigarette smoking and alcohol consumption were observed to be positively associated with cancer fo the pharynx. By contrast, increasing intake of certain fruits and vegetables, notably oranges, tangerines and Chinese white radishes, appeared to be associated with a reduced risk for cancer of the pharynx.

(c) Meta-analyses

The IOM (2006) conducted a meta-analysis of the published cohort studies examining the association between asbestos exposure and cancer of the pharynx. The IOM noted that the findings of the cohort studies were consistently positive. They calculated that the "estimated aggregated relative risk of cancer of the pharynx from any exposure to asbestos was 1.44 (95%CI: 1.04–2.00). "The IOM noted that few studies had evaluated dose–response trends, and that there was no indication of higher risks associated with more extreme exposures."

The IOM also conducted a meta-analysis of the case–control studies examining the association between asbestos exposure and cancer of the pharynx. The IOM reported the summary relative risk for cancer of the pharynx in people with "any" exposure to asbestos compared to people with no exposure to be 1.5 (95%CI: 1.1–1.7). The IOM observed that the studies were inconsistent, and that there was little evidence for a dose–response relationship.

2.4.2 Cancer of the larynx

See Table 2.5 online.

Cancer of the larynx in relation to asbestos exposure has been studied in a large number of cohort and case–control studies undertaken among occupationally exposed populations in North and South America, Europe, and Asia. (IOM, 2006).

(a) Cohort studies

Cohort studies of workers exposed occupationally to asbestos have found evidence for an association between asbestos exposure and cancer of the larynx across a broad range of industries. The Working Group reviewed 29 cohort studies encompassing 35 populations exposed to asbestos. Noteworthy findings from among these studies are summarized in the following paragraphs.

Selikoff & Seidman (1991) found an SMR for cancer of the larynx of 1.70 (95%CI: 1.01–1.69) among 17800 male insulation workers in the USA and Canada.

Musk *et al.* (2008) found an SMR for cancer of the larynx of 1.56 (95%CI: 0.83–2.67) among 6943 asbestos miners and millers from Western Australia, exposed predominantly to crocidolite

asbestos, when all cohort members lost to follow-up were assumed to be alive. When the analysis was re-run censoring all subjects at the date last know to be alive, the SMR was 2.57 (95%CI: 1.37–4.39).

Reid *et al.* (2004) carried out a study of cancer incidence in this same Australian cohort, and found a significant increase in incidence of cancer of the larynx (SIR, 1.82; 95%CI: 1.16–2.85).

Piolatto *et al.* (1990) found an SMR for cancer of the larynx of 2.67 (95%CI: 1.15–5.25; based on eight deaths) in a cohort study of 1058 male asbestos miners in northern Italy. In the subset of this cohort with > 20 years' exposure to asbestos, the SMR for cancer of the larynx was 4.55 (95%CI: 1.47–10.61). There was evidence of a positive dose–response relationship between cumulative exposure to asbestos dust, measured as fibre–years, and risk of death from cancer of the larynx. The SMRs for cancer of the larynx were 1.43 (95%CI: 0.04–7.96) in workers with exposure < 100 fibre–years; 2.22 (95%CI: 0.27–8.02) in workers with exposure of 100–400 fibre–years; and 3.85 (95%CI: 1.25–8.98) in workers with cumulative exposure > 400 fibre–years.

Peto *et al.* (1985) found an overall SMR for cancer of the larynx of 1.55 (95%CI: 0.42–3.97; based on four deaths) in a cohort of 3211 asbestos-textile workers in the United Kingdom. When workers were subdivided according to time since first employment, and by duration of employment in "scheduled" (asbestos-exposed) areas of the plant, four deaths from cancer of the larynx were observed in the most heavily exposed group versus 1.53 expected (SMR, 2.55).

Pira *et al.* (2005) found an overall SMR for cancer of the larynx of 2.38 (95%CI: 0.95–4.90; based on seven deaths–all of them in male workers) in a cohort of 889 men and 1077 women employed in an asbestos textiles plant in Italy.

Raffn *et al.* (1989) found an overall SIR for cancer of the larynx of 1.66 (95%CI: 0.91–2.78) in a cohort study of 7986 men and 584 women employed in the asbestos-cement industry in Denmark However, in the subset with > 5 years employment, the SIR was 2.27 (95%CI: 0.83–4.95), and in the group first employed from 1928–40, the SIR was 5.50 (95%CI: 1.77–12.82).

(b) Case–control studies

Case–control studies are important in examining relationships between asbestos exposure and cancer of the larynx, because they overcome the relative rarity of the diagnosis in cohort studies, and also because they permit consideration of potential confounding by exposure to tobacco and alcohol, the two most important risk-factors for this malignancy in developed and developing countries.

The Working Group analysed 15 case–control studies of asbestos and cancer of the larynx. This analysis revealed that 14 of the 15 published studies had found evidence for a significantly positive association between asbestos exposure and cancer of the larynx; only one study (Luce *et al.*, 2000) reported an odds ratio below 1.0.

(c) Meta-analyses

The IOM conducted a meta-analysis of cohort studies examining the association between asbestos exposure and cancer of the larynx. For studies examining "any" versus no exposure, the summary relative risk was 1.4 (95%CI: 1.19–1.64). For studies comparing "high" exposure versus no exposure, the lower bound summary relative risk was 2.02 (95%CI: 1.64–2.47), and the upper bound summary relative risk was 2.57 (95%CI: 1.47–4.49).

The IOM also conducted a meta-analysis of the published case–control studies examining the association between asbestos exposure and cancer of the larynx (IOM, 2006). This meta-analysis calculated a summary relative risk of 1.43 (95%CI: 1.15–1.78), before adjusting for consumption of tobacco and alcohol. After adjusting for tobacco and alcohol consumption, the association of cancer of the larynx with

asbestos exposure persisted, with an adjusted summary relative risk of 1.18 (95%CI: 1.01–1.37).

2.4.3 Cancer of the oesophagus

See Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.6.pdf.

(a) Cohort studies

The Working Group examined 25 studies of cohorts occupationally exposed to asbestos. Notable findings from among these studies are:

Selikoff & Seidman (1991) found an SMR for cancer of the oesophagus of 1.61 (95%CI: 1.13–2.40) among a cohort of 17800 asbestos insulations workers across the USA and Canada. Selikoff & Seidman (1991) observed that cancer in asbestos workers is "very much related to latency," with most of the increased risk occurring only 25 or more years from the onset of occupational exposure to asbestos.

In a cohort of 10939 male and 440 female asbestos miners and millers in Quebec, Canada, exposed predominantly to chrysotile asbestos, followed through 1975, McDonald *et al.* (1980) reported that mortality for cancer of the oesophagus and stomach (the two were combined) was elevated (SMR, 1.27). Further follow-up through 1988 of a subset of this cohort, consisting of 5335 men, examined esophageal cancer mortality separate from stomach cance,r and found no excess mortality (SMR, 0.73; 95%CI: 0.35 – 1.34) (McDonald *et al.*, 1993).

Musk *et al.* (2008) found an SMR for cancer of the oesophagus was 1.01 (95%CI: 0.71–1.40) in a cohort study of 6943 asbestos miners from Western Australia followed through 2000, exposed predominantly to crocidolite asbestos, when all cohort members lost to follow-up were assumed to be alive. When the analysis was re-run censoring all subjects at the date last known to be alive, the SMR was 1.20 (95%CI: 0.62–2.10).

Hein *et al.* (2007) found an SMR for cancer of the oesophagus of 1.87 (95%CI: 1.09–2.99) in a cohort of 3072 asbestos textile workers in South Carolina, occupationally exposed to chrysotile asbestos and followed through 2001.

Peto *et al.* (1985) found 11 deaths from cancer of the oesophagus versus 6.59 expected (SMR = 1.67; 95%CI: 0.83–2.99) in a cohort of 3211 male asbestos textile workers in the United Kingdom. For the subset of workers with 10+ years employment in "scheduled" (asbestos-exposed) areas of the plant and with 20+ years since first employment, the SMR for cancer of the oesophagus was 2.36 (95%CI: 0.49–6.91). For all workers in this cohort with < 20 years since first employment, two deaths for cancer of the oesophagus was observed versus 2.18 expected, and for workers with 20+ years since first employment, there were nine deaths from cancer of the oesophagus versus 4.4 expected (see Table 6 in Peto *et al.*, 1985).

Berry *et al.* (2000) found a 2-fold excess mortality for cancer of the oesophagus (SMR, 2.08; 95%CI: 1.07–3.63) among a cohort of over 5000 asbestos-exposed factory workers in the east end of London, United Kingdom, who had produced asbestos insulation boards, and who were followed for 30+ years. In the subset of workers within this population with "severe" asbestos exposure of more than 2 years' duration, the SMR for cancer of the oesophagus was 5.62 (95%CI: 1.82 – 13.11). And in the subset of women with "severe" exposure to asbestos of > 2 years, the SMR for cancer of the oesophagus was 9.09 (95%CI: 1.10–32.82).

Other cohort studies of various groups occupationally exposed to asbestos – asbestos-cement workers, friction products workers, and "generic" asbestos workers – yield generally non-positive results for cancer of the oesophagus.

(b) Case–control studies

The Working Group examined five case–control studies that examined the association between asbestos exposure and cancer of the oesophagus.

A case–control study in Quebec, Canada found an OR of 2.0 (95%CI: 1.1–3.8) for any exposure to asbestos among 17 patients diagnosed with squamous cell carcinoma of the oesophagus. (Parent *et al.*, 2000).

A case–control study conducted within a cohort of nearly 400000 Swedish construction workers found evidence for a positive association between asbestos exposure and adenocarcinoma of the oesophagus. Relative risk increased from 1.0 (reference) among workers with no asbestos exposure, to 1.7 (95%CI: 0.5–5.4) among those with "moderate" exposure, and to 4.5 (95%CI: 1.4–14.3) among those workers with "high" asbestos exposure, thus suggesting a positive dose–response relationship (Jansson *et al.*, 2005).

(c) Meta-analyses

Meta-analyses have been undertaken of the association between asbestos exposure and cancer of the oesophagus:

A meta-analysis by Frumkin & Berlin (1988) stratified studies according to SMR for lung cancer and also according to the percentage of deaths due to mesothelioma. The rationale is that a higher death rate for either lung cancer or mesothelioma is taken to be a surrogate index of higher cumulative exposure to asbestos. However, no association was observed between death rate for cancer of the oesophagus in the published cohorts by either lung cancer SMR or percentage of death for mesothelioma.

Meta-analyses by Edelman (1988) and by Goodman *et al.* (1999) did not detect an association between asbestos exposure and cancer of the oesophagus.

A meta-analysis by Morgan *et al.* (1985) that examined earlier studies, which tended to have heavier exposure, found a summary SMR for cancer of the oesophagus in asbestos-exposed workers of 2.14 (95%CI: 1.326–3.276). When cases of cancer of the oesophagus based on "best evidence" (pathological review) were deleted from these cohorts, the SMR remained elevated at 2.38 (95%CI: 1.45–3.68).

The IOM (2006) conducted a meta analysis of 25 cohort studies and reported a summary relative risk of 0.99 (95%CI: 0.78–1.27) for any exposure to asbestos versus no exposure. The IOM also examined the relative risk of "high" versus no exposure, and calculated a lower bound summary relative risk of 1.35 (95%CI: 0.81–2.27), and a higher bound summary relative risk of 1.43 (95%CI: 0.79–2.58). The IOM determined that there were too few case–control studies to permit a meta-analysis.

2.4.4 Cancer of the stomach

The Working Group reviewed 42 cohort studies and five population-based case–control studies that examined the association between asbestos and cancer of the stomach (See Table 2.6 online).

(a) Cohort studies

Notable findings among the cohort studies are:

Selikoff *et al.* (1964) reported a nearly 3-fold excess mortality for cancer of the stomach (12 observed versus 4.3 expected) in a population of 632 insulation workers in New York and New Jersey occupationally exposed to asbestos dust. Further analysis within this cohort (Selikoff *et al.*, 1979) found evidence of a dose–response relationship between duration of exposure to asbestos (in years), and risk of death from cancer of the stomach. The SMR for cancer of the stomach increased from 0.00 in workers exposed for < 20 years, to 4.00 (95%CI: 1.47 – 8.71) in those exposed for 20 –35 years, and to 3.42 (95%CI: 1.82 – 5.85) in those exposed for > 35 years.

Selikoff *et al.* (1967) found a modest, non-significant increase in risk of death for cancer of the stomach: 34 observed v. 29.4 expected, (SMR = 1.16;95%CI: 0.92 – 1.78) in a larger cohort study of 17800 insulation workers across the USA and Canada. No data on dose–response for cancer of the stomach were presented in this analysis.

Liddell *et al.* (1997) reported an overall SMR for cancer of the stomach of 1.24 (95%CI: 1.07 –1.48) in a study of 10918 asbestos miners and millers exposed predominantly to chrysotile asbestos, in Quebec, Canada. Within this cohort, a positive dose–response relationship was observed between cumulative exposure to asbestos dust (mcpf-year) and mortality for cancer of the stomach. Thus, for workers with cumulative dust exposure < 300, the SMR was 1.16; for workers with cumulative exposure of 300 – 400, the SMR was 1.29; for workers with cumulative exposure of 400 – 1000, the SMR was 1.21; and for workers in the highest exposure category, with cumulative exposure > 1000, the SMR was 3.21 (95%CI: 1.87 –5.14). An additional finding in this cohort was a modest interaction between cumulative asbestos exposure, cigarette smoking, and mortality from cancer of the stomach.

Musk *et al.* (2008) found an SMR for cancer of the stomach of 1.01 (95%CI: 0.71 – 1.40) in a cohort of 6943 asbestos miners and millers exposed predominantly to crocidolite asbestos in Wittenoom, Western Australia, followed through the end of 2000, and when all cohort members lost to follow-up were assumed to be alive. When the analysis was re-run censoring subjects at the date last known to be alive, the SMR was 1.71 (95%CI: 1.20–2.35).

Reid *et al.* (2004) conducted a nested case–control study within this same Australian cohort, and found a positive exposure-response relationship between cancer of the stomach and cumulative exposure to asbestos (test for trend, $P = 0.057$). No association was seen between cancer of the stomach and either time since first exposure or year of starting work with asbestos. Smoking status was associated with cancer of the stomach, but not significantly.

Meurman *et al.* (1974) found a non-significant increase in SMR for cancer of the stomach: SMR = 1.42 (95%CI: 0.76 – 2.43) in a cohort of 736 asbestos miners in Finland exposed to anthophyllite asbestos.

Berry *et al.* (2000) found a modest, non-significant increased risk for death from cancer of the stomach: 28 observed versus 23.1 expected (SMR, 1.21; 95%CI: 0.81–1.75) in a British study of factory workers producing asbestos insulation in the east end of London.

Strongly positive dose–response associations between cumulative asbestos response and cancer of the stomach were observed in two cohort studies of Chinese factory workers – one in Beijing and the other in Qingdao; relative risks for cancer of the stomach were 4.4 and 2.4, respectively (Zhu & Wang, 1993; Pang *et al.*, 1997).

Raffn *et al.* (1989) observed 43 deaths from cancer of the stomach versus 30.09 expected (SMR, 1.43; 95%CI: 1.03 – 1.93) in a cohort of 7986 men employed from 1928–84 in the asbestos cement industry in Denmark.

Enterline *et al.* (1987) observed a SMR for cancer of the stomach of 1.80 (95%CI: 1.10–2.78) in a cohort of 1074 retired US asbestos workers.

Epidemiological studies of cohorts with asbestos-related diseases – asbestosis and benign pleural disease – have not found increased mortality for cancer of the stomach (Germani *et al.*, 1999; Karjalainen *et al.*, 1999; Szeszenia-Dabrowska *et al.*, 2002).

(b) Case–control studies

Case–control studies exploring the relationship between asbestos exposure and cancer of the stomach yield inconsistent results. The Working Group reviewed five case–control studies. Notable findings are these:

A study from Poland (Krstev *et al.*, 2005) found an OR for cancer of the stomach of 1.5 (95%CI: 0.9–2.4) for workers ever exposed to asbestos, and of 1.2 (95%CI: 0.6–2.3) for workers with 10 or more years of exposure to asbestos.

The largest case–control study to examine the association between asbestos and cancer of the stomach (Cocco *et al.*, 1994) reported an odds ratio of 0.7 (95%CI: 0.5–1.1) for workers ever exposed to asbestos, and of 1.4 (95%CI: 0.6–3.0) for those with 21+ years of exposure to asbestos.

The most strongly positive case–control study linking asbestos to cancer of the stomach is the case–control study, cited above, nested within the Western Australia mining cohort (Reid *et al.*, 2004).

(c) Meta-analyses

Several meta-analyses have been undertaken of the association between asbestos exposure and cancer of the stomach.

A meta-analysis by Frumkin & Berlin (1988) stratified studies according to SMR for lung cancer and also according to percentage of deaths due to mesothelioma. Frumkin & Berlin found in cohorts where the SMR for lung cancer was < 2.00 that the SMR for cancer of the stomach was 0.91 (95%CI: 0.71–1.16). By contrast, when the SMR for lung cancer was > 2.00, the SMR for cancer of the stomach increased to 1.34 (95%CI: 1.07–1.67).

Gamble (2008) reported that point estimates for cancer of the stomach mortality tended towards 1.0 when the excess risk for lung cancer were less than 4-fold, but "tended to be somewhat elevated when lung cancer relative risks were 4-fold or greater." Gamble observed further that "combined relative risks for cancer of the stomach stratified by lung cancer categories showed a suggestive trend, with a significant deficit (0.80) when lung cancer SMRs were <1.0 that increased monotonically to a significant 1.43-fold excess in the studies with lung cancer SMRs > 3.0." Gamble observed no trend for increasing SMR for cancer of the stomach with increasing percentage of deaths from mesothelioma (Gamble, 2008).

The IOM (2006) conducted a meta-analysis of 42 cohort studies examining the association between asbestos exposure and cancer of the stomach. The IOM noted that the "majority of cohort relative risk estimates for cancer of the stomach exceed the null value (1.0), indicating excesses, although estimates varied considerably in strength." In cohorts that compared "any" versus no exposure, the summary relative risk was 1.17 (95%CI: 1.07–1.28). The IOM notes that with respect to dose–response, the summary estimates were stable. Thus in the cohorts that compared "high" versus no exposure, the lower bound summary relative risk was 1.31 (95%CI: 0.97–1.76), and the higher bound summary relative risk, 1.33 (95%CI: 0.98–1.79).

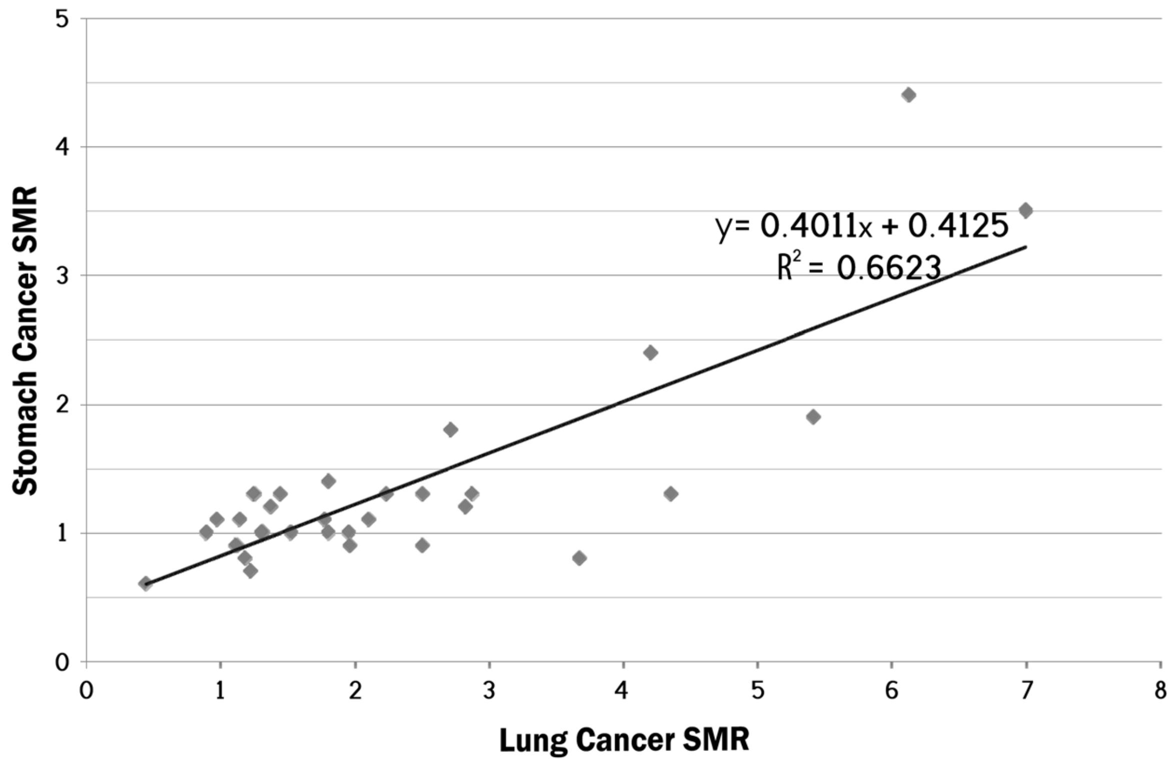
The IOM conducted a meta-analysis of the five case–control studies resulting in a combined relative risk of 1.11 (95%CI: 0.76–1.64). The summary odds ratio increased when only extreme exposure was considered (OR, 1.42; 95%CI: 0.92–2.20)

The Working Group developed a scatter plot comparing SMRs for lung cancer with SMRs for cancer of the stomach in the same cohorts. A positive trend was observed between the two, and the correlation coefficient (r2) = 0.66, see Fig. 2.1.

(i) Asbestos in drinking-water and cancer of the stomach

Ecological correlational studies conducted from the 1960s into the early 1980s suggested an association between asbestos in drinking-water and cancer of the stomach. These studies correlated population exposure to asbestos in water supplies with population cancer rates. Levy *et al.* (1976) reported an excess in cancer of the stomach among persons in Duluth, MN, USA exposed to taconite asbestos in drinking-water. Wigle (1977) saw an excess of male cancer of the stomach among some exposed to asbestos in drinking-water in Quebec. Conforti *et al.* (1981)

Fig 2.1 Stomach & lung cancer correlation in asbestos cohorts



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saw a similar association in the San Francisco Bay area, USA. Polissar *et al.* (1982) examined cancer incidence and mortality among residents of the Puget Sound area, USA, in relation to asbestos in regional drinking-water. They observed no association between asbestos exposure and cancer of the stomach. A similarly negative study was observed in a study conducted in Woodstock, NY, USA (Howe *et al.*, 1989).

Kjærheim *et al.* (2005) examined cancer of the stomach incidence in Norwegian light-house keepers exposed to asbestos in drinking-water. They found an SIR for cancer of the stomach in the entire cohort of 1.6 (95%CI: 1.0–2.3). In the subcohort with "definite" exposure to asbestos, the SIR was 2.5 (95%CI: 0.9–5.5). In those members of the definite exposure subcohort followed for 20+ years, the SIR was 1.7 (95%CI: 1.1–2.7).

Cantor (1997) conducted a systematic review of the epidemiological literature on exposure to asbestos in drinking-water and cancer of the stomach, and concluded that the available data were inadequate to evaluate the cancer risk of asbestos in drinking-water.

Marsh (1983) conducted a critical analysis of 13 epidemiological studies of asbestos and drinking-water conducted in the USA and Canada, and found no consistent pattern of association.

2.4.5 Cancer of the colorectum

The Working Group examined data from 41 occupational cohorts and 13 case–control studies that reported data on associations between asbestos exposure and cancer of the colon and rectum (See Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.7.pdf). The Working Group made the decision to combine information on these two sites, although a few comments in several places in the text about the two sites considered separately have also been made.

(a) Cohort studies

An association between occupational exposure to asbestos and cancer of the colorectum was first reported in 1964 by Selikoff *et al.* in a cohort of 632 male insulation workers in New York and New Jersey, USA (Selikoff *et al.*, 1964). Further analysis of this cohort found a positive relationship between duration of work with asbestos and risk of cancer of the colorectum, in that the SMR increased from 0.00 (95%CI: 0.00–18.45) in workers with < 20 years exposure, to 3.68 (95%CI: 1.48–7.59) among workers with 20–35 years' exposure, and to 2.58 (95%CI: 1.48–4.19) among workers with the longest duration of exposure, > 35 years (Selikoff & Hammond, 1979).

Selikoff *et al.* (1967), in a second report, found an association between occupational exposure to asbestos and cancer of the colorectum in a population of 17800 asbestos insulators across the USA and Canada (SMR, 1.37; 95%CI: 1.14–1.64).

Seidman *et al.* (1986) reported an elevated mortality from cancer of the colorectum in a population of 820 male factory workers in Paterson, NJ, USA, exposed to amosite asbestos (SMR, 2.77; 95%CI: 1.16–2.80). They noted that cancer of the colorectum in asbestos workers tended to be a disease of long latency; they reported that the ratio of observed to expected deaths increased with increasing interval since initial exposure to asbestos.

McDonald *et al.* (1980) reported an overall SMR for cancer of the colorectum of only 0.78 in a study of 10939 men and 440 women workers employed as asbestos miners and millers in Quebec with predominant exposure to chrysotile asbestos. Additionally, however, McDonald *et al.* reported a "clear trend for SMRs to be higher, the heavier the exposure." Thus with increasing levels of cumulative occupational exposure to asbestos dust, relative risks for cancer of the colorectum increased in this cohort from 1.00 in workers with less than 30 mpcf–y cumulative exposure, to 0.93 in workers with 30–300 mpcf–y, to 1.96 in workers with 300–1000 mpcf–y, and then in the group with heaviest exposure, > 1000 mpcf–y, to 5.26.

Albin *et al.* (1990) found an overall SMR for cancer of the colorectum of only 1.5 (95%CI: 0.7–3.0) in a cohort of 1465 asbestos-cement workers in Sweden. A positive association between asbestos exposure and cancer of the colorectum was reported, but when cancer of the colorectum mortality was examined by individual cumulative exposure to asbestos, measured as fibre–years/mL, the SMR was 1.3 (95%CI: 0.5–2.9) for those workers with cumulative exposure of < 15 fibre–years/mL; for those with cumulative exposure of 15–39 fibre–years/mL, the SMR was 1.1(95%CI: 0.3–3.9); and for those workers in highest exposure category with > 40 fibre–years/mL, the SMR for cancer of the colorectum was 3.4 (95%CI: 1.2–9.5). Diagnosis in all but one of the cancers in the highest exposure category was verified by pathological review, and no case of certified or probable mesothelioma was found. The trend towards increasing mortality from cancer of the colorectum with increasing cumulative exposure to asbestos was statistically significant ($P = 0.04$). A similar trend was seen for cancer of the colorectum morbidity.

Excess mortality from colon cancer was observed in a heavily exposed cohort of over

5000 workers in the east end of London, who had produced asbestos insulation board and were followed for 30+ years (Berry *et al.*, 2000). The overall SMR for colon cancer in this cohort was 1.83 (95%CI: 1.20–2.66). There was evidence for a positive dose–response relationship, in that excess mortality from colon cancer was confined to men who had worked as laggers or had been severely exposed for more than 2 years. This positive trend was statistically significant ($P = 0.017$).

In a cohort comprised of family members of men who had been employed in an asbestos-cement factory in Casale Monferrato, Italy, Ferrante *et al.* (2007) examined cancer mortality. Among women with domestic exposure to asbestos, 21 deaths from cancer of the "intestine and rectum" versus 16.0 expected (SMR, 1.31; 95%CI: 0.81–2.0) were observed. For cancer of the rectum, ten deaths versus five expected (SMR, 2.00; 95%CI: 0.96–3.69) were observed.

Several other cohort studies of occupationally exposed populations in a variety of industries have also found evidence for an association between asbestos exposure and cancer of the colorectum (Puntoni *et al.*, 1979: Hilt *et al.*, 1985; Jakobsson *et al.*, 1994; Raffn *et al.*, 1996; Szeszenia-Dabrowska *et al.*, 1998; Smailyte *et al.*, 2004).

Jakobsson *et al.* (1994) examined colon cancer by anatomical location in asbestos-cement workers, and observed an increased incidence of malignancy in the right side of the colon, but not in the left side.

A report on incidence of cancer of the colorectum from the Beta-Carotene and Retinol Efficacy Trial (CARET) found a relative risk of 1.36 (95%CI: 0.96–1.93) among 3987 heavy smoker participants occupationally exposed to asbestos as compared to smoker participants not exposed to asbestos (Aliyu *et al.*, 2005). Of note was the finding that the relative risk for cancer of the colorectum was 1.54 (95%CI: 0.99–2.40) among participants with asbestos-induced pleural plaques. The investigators interpreted the presence of pleural plaques as a marker for heavy individual exposure to asbestos. Risk for cancer of the colorectum also increased with worsening pulmonary asbestosis ($P = 0.03$ for trend). It was reported that a "dose–response trend based on years of asbestos exposure was less evident".

(b) Case–control studies

Evidence from case–control studies of asbestos and cancer of the colorectum is in general less strong than the evidence from the cohort studies. However, case–control studies from the Nordic countries and the USA have, however, reported significant increases in asbestos-associated odds ratios in occupationally exposed poulations (Fredriksson *et al.*, 1989; Gerhardsson de Verdier *et al.*, 1992; Vineis *et al.*, 1993; Kang *et al.*, 1997; Goldberg *et al.*, 2001).

Consideration of latency since first exposure appears to be an important factor in assessing these studies. Thus, Gerhardsson de Verdier *et al.* (1992) examined incidence of cancer of the colorectum by interval since first occupational exposure and observed "for subjects exposed to asbestos, the risks were highest when the latency period was more than 39 years." Gerhardsson de Verdier *et al.* observed further that the relative risk for cancer of the right colon was 2.6 (95%CI: 1.2–5.9) among workers exposed to asbestos, and that for malignancy of the left colon, only 0.5 (95%CI: 0.1–1.9).

Other cohort and case–control studies have not found evidence for an association between asbestos exposure and cancer of the colorectum (Gardner *et al.*, 1986; Hodgson & Jones, 1986; Garabrant *et al.*, 1992; Dement *et al.*, 1994; Demers *et al.*, 1994; Tulchinsky *et al.*, 1999; Hein *et al.*, 2007; Loomis *et al.*, 2009).

(c) Meta-analyses

Some of these meta-analyses have stratified studies according to the standardized mortality ratio for lung cancer or the percentage of deaths due to mesothelioma:

Morgan *et al.* (1985) found a summary standardized mortality ratio for cancer of the colorectum of 1.13 (95%CI: 0.97–1.30). This was reduced to 1.03 (95%CI: 0.88–1.21) after deleting cases in which the diagnosis of cancer of the colorectum was based on "best evidence" (pathological review) rather than death certificate data.

Frumkin & Berlin (1988) found in cohorts where the standardized mortality ratio for lung cancer was < 2.00 that the standardized mortality ratio for cancer of the colorectum was 0.86 (95%CI: 0.69–1.09). By contrast, when the standardized mortality ratio for lung cancer was > 2.00, the standardized mortality ratio for cancer of the colorectum increased to 1.61 (95%CI: 1.34–1.93).

Homa *et al.* (1994) found an elevated summary standardized mortality ratio for cancer of the colorectum in cohorts exposed to serpentine asbestos that had an standardized mortality ratio for lung cancer > 2.00 (summary standardized mortality ratio for cancer of the colorectum, 1.73; 95%CI: 0.83–3.63), and also in cohorts exposed to a mix of amphibole and serpentine asbestos that had a standardized mortality ratio for lung cancer > 2.00 (summary standardized mortality ratio for cancer of the colorectum, 1.48; 95%CI: 1.24–1.78). Among cohorts exposed to amphibole asbestos, the standardized mortality ratio for cancer of the colorectum was elevated regardless of the standardized mortality ratio for lung cancer. Homa *et al.* (1994) saw similar trends between standardized mortality ratio for cancer of the colorectum and percentage of deaths from mesothelioma.

Gamble (2008) reported that there was "tendency for CRC [cancer of the colorectum] risk ratios to be elevated when lung cancer risk ratios are >4" and further noted a significantly elevated standardized mortality ratio of 1.60 (95%CI: 1.29–2.00) for cancer of the colorectum when the standardized mortality ratio for lung cancer exceeds 3.00. Gamble (2008) observed no trend in cancer of the colorectum mortality with increasing percentage of deaths due to mesothelioma. Gamble saw no association between asbestos exposure and rectal cancer.

The IOM (2006) conducted a meta-analysis of cohort studies examining the association between asbestos exposure and cancer of the colorectum. In studies that compared "any" versus no exposure, the summary relative risk was 1.15 (95%CI: 1.01–1.31). For studies comparing "high" versus no exposure, the lower-bound summary relative risk was 1.24 (95%CI: 0.91–1.69), and the upper-bound summary relative risk, 1.38 (95%CI: 1.14–1.67).

The IOM also conducted a meta-analysis of the published case–control studies. Overall, 13 studies comparing "any" versus no exposure yielded a summary relative risk of 1.16 (95%CI: 0.90–1.49).

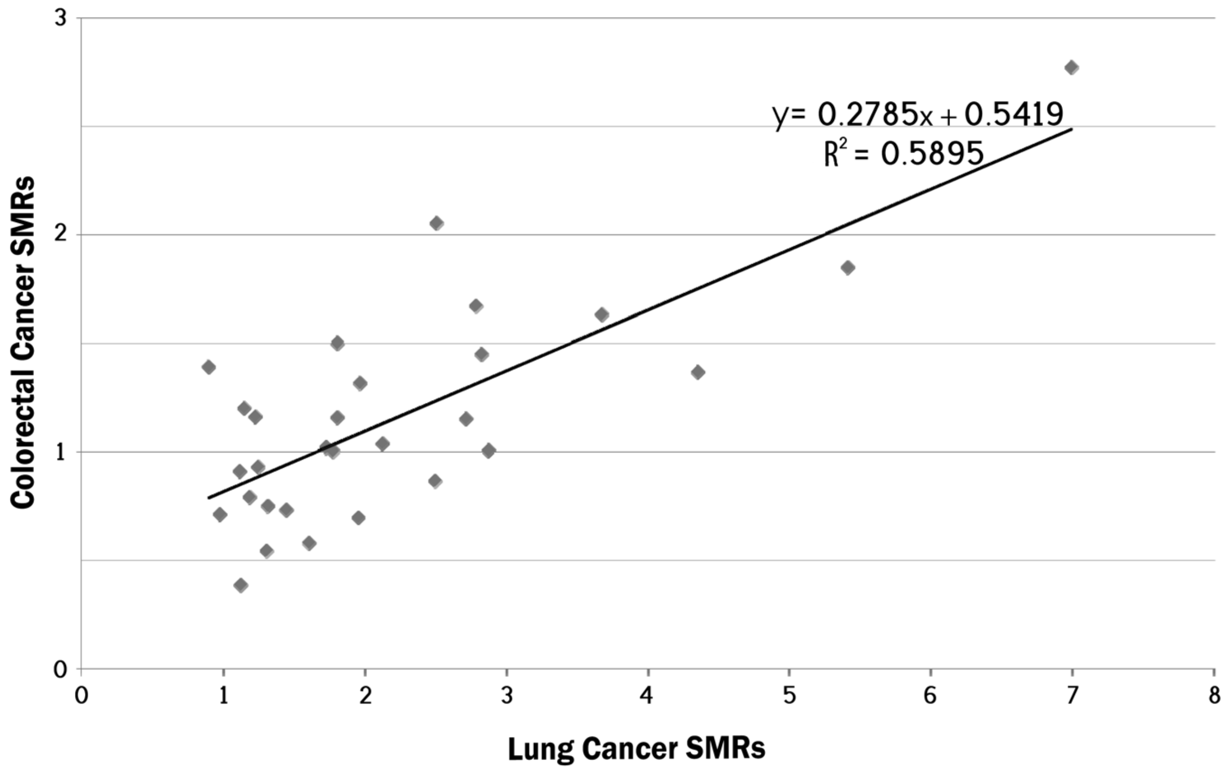
The *IARC Monograph* 100C Working Group developed a scatter plot comparing standardized mortality ratios for lung cancer with standardized mortality ratios for cancer of the colorectum in the same cohorts. The trend was positive with a correlation coefficient (r2) of 0.59, see Fig. 2.2.

(i) Asbestos in drinking-water and cancer of the colorectum

Ecological correlational studies conducted from the 1960s into the early 1980s suggested an association between asbestos in drinking-water and cancer of the colon. These studies correlated population exposure to asbestos in water supplies with population cancer rates. Polissar *et al.* (1982) examined cancer incidence and mortality among residents of the Puget Sound area, USA, in relation to asbestos in regional drinking-water. No association between asbestos exposure and colon cancer was observed. A similarly negative study was observed in a study conducted in Woodstock, NY, USA (Howe *et al.*, 1989).

Kjærheim *et al.* (2005) examined colon cancer incidence in Norwegian light-house keepers exposed to asbestos in drinking-water. The standardized incidence ratio for colon cancer in

Fig 2.2 Colorectal & lung cancer correlation in asbestos cohorts



Compiled by the Working Group

the entire cohort was 1.5 (95%CI: 0.9–2.2). In the subcohort with "definite" exposure to asbestos, the standardized incidence ratio was 0.8 (95%CI: 0.1–2.9). In those members of the definite exposure subcohort followed for 20+ years, the standardized incidence ratio was 1.6 (95%CI: 1.0–2.5).

Cantor (1997) conducted a systematic review of the epidemiological literature on exposure to asbestos in drinking-water and colon cancer and concluded that the data were inadequate to evaluate colon cancer risk of asbestos in drinking-water.

Marsh (1983) conducted a critical analysis of 13 epidemiological studies of asbestos and drinking-water conducted in the USA and Canada and found no consistent pattern of association.

2.4.6 Cancer of the ovary

The published literature examining the association between asbestos exposure and cancer of the ovaries is relatively sparse, because the workforce occupationally exposed to asbestos in such occupations as mining, milling shipyard work, construction and asbestos insulation work has been predominantly male. An examination of the association between asbestos and ovarian cancer was not undertaken by the IOM (2006).

See Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.8.pdf.

(a) Cohort studies

The Working Group examined 11 cohort studies that examined the association between asbestos exposure and ovarian cancer in 13 populations, ten with occupational exposure to asbestos and three with community-based or residential exposure.

Acheson *et al.* (1982) examined a cohort in the United Kingdom consisting of two groups of women in separate factories (n = 1327), employed in the manufacture of asbestos-containing gas masks before and during World War II. One factory had used crocidolite asbestos, and the other had used chrysotile. Among 757 women in the plant that used crocidolite, 12 deaths from ovarian cancer were observed versus. 4.4 expected (SMR, 2.75; 95%CI: 1.42–4.81). Among 570 women in the plant that used chrysotile asbestos, five deaths were observed for ovarian cancer versus 3.4 expected (SMR, 1.48; 95%CI: 0.48–3.44).

Wignall & Fox (1982) conducted a 30-year, follow-up mortality study of a population of 500 women in the United Kingdom employed in the manufacture of asbestos-containing gas masks before and during World War II. The type of asbestos used was crocidolite. A total of six deaths from ovarian cancer were obserevd versus. 2.8 expected (SMR, 2.13). When the cohort was subdivided according to degree of exposure to asbestos, the highest mortality from ovarian cancer was found among the subgroup definitely exposed to asbestos from the early 1940s (SMR, 14.81; $P < 0.01$). Overall five deaths from ovarian cancer were found among women definitely exposed to asbestos (versus 0.63 expected), whereas none were found among women definitely not exposed to asbestos (versus 0.40 expected).

To address potential misclassification of some deaths in this cohort recorded on death certificates as ovarian cancer as opposed to peritoneal mesothelioma, Wignall & Fox (1982) conducted a histopathological review of the cases cases of diagnosed ovarian cancer for which tissue material was available. One of these three cases was found to be peritoneal mesothelioma, while the diagnosis of ovarian cancer was sustained in the other two cases.

In a cohort study of 700 women factory workers employed in an asbestos-board insulation manufacturing company in the east end of London and followed for 30+ years, Berry *et al.* (2000) observed nine deaths from ovarian cancer versus 3.56 expected (SMR, 2.53; 95%CI: 1.16–4.80) (Berry *et al.*, 2000), with evidence for a positive exposure–response relationship. Among women with low-to-moderate exposure to asbestos, two deaths were observed versus 0.54 expected; in the subset with "severe" asbestos exposure of < 2 years' duration, two deaths were observed versus 2.12 expected. (SMR, 0.94); and among women with severe exposure of > 2 years' duration, five deaths from ovarian cancer were observed versus 0.90 expected (SMR, 5.35).

An assessment was performed of the significance of the positive exposure–response trend (P = 0.18). To address the potential misclassification of some deaths in this cohort having been recorded as ovarian cancer as opposed to peritoneal mesothelioma, Newhouse *et al.* (1972) conducted a histopathological review of the four deaths that by 1972 had been recorded as due to ovarian cancer; three of the four had occurred in women with severe and prolonged exposure to asbestos. Histological material was available for two of these cases. In both, the diagnosis of ovarian cancer was confirmed.

Reid *et al.* (2008) reported on cancer mortality in a cohort of 2552 women and girls who lived in the crocidolite asbestos mining town of Wittenoom in Western Australia during 1943–92, who were not involved in asbestos

mining and milling. Environmental contamination of the town with asbestos dust is reported to have been extensive. The women's exposure was environmental and not occupational. There were nine deaths from ovarian cancer in this cohort (SMR, 1.26; 95%CI: 0.58–2.40).

Reid *et al.* (2009) conducted a cancer incidence study in the same cohort of 2552 women and girls in Western Australia with environmental exposure to crocidolite asbestos. Additionally, they examined cancer incidence in 416 women who had worked in various capacities in the Wittenoom crocidolite asbestos mines and mills. Among community residents, ten incident cases of ovarian cancer were observed (SIR, 1.18; 95%CI: 0.45–1.91). Among women workers employed in the asbestos factory, one case of ovarian cancer was observed (SIR, 0.49; 95%CI: 0.01–2.74).

To address the possibility that some diagnosed cases of ovarian cancer in this cohort might in fact have been cases of peritoneal mesothelioma, Reid *et al.* (2009) examined pathological material from nine of their cases. The diagnosis of ovarian cancer was sustained in every case.

Pira *et al.* (2005) conducted a cohort study of 1077 women employed for at least one month during 1946–84 in an asbestos-textile factory in Italy, and followed up to 1996. A variety of types of asbestos were used in the factory, including crocidolite. A non-significantly increased standardized mortality ratio of 2.61 was observed for cancer of the ovary, based on five deaths. Among women in this cohort with ≥ 10 years of employment with asbestos, the standardized mortality ratio for ovarian cancer was 5.73, based on three deaths. Among women with ≥ 35 years since first employment, the standardized mortality ratio for ovarian cancer was 5.37, based on two deaths. This cohort was heavily exposed to asbestos, as supported by a standardized mortality ratio for lung cancer among women of 5.95, and by the occurrence of 19 deaths from mesothelioma (12%) among 168 total deaths in women.

Magnani *et al.* (2008) examined cancer mortality among a cohort of former workers at a now closed asbestos-cement factory in Casale Monferrato, Italy. A mix of crocidolite and chrysotile asbestos was used in this factory. Among women workers, there was an excess of ovarian cancers: nine observed versus 4.0 expected (SMR, 2.27; $P < 0.05$). Among women workers with 30 or more years exposure, the standardized mortality ratio for ovarian cancer was 2.97. Bertolotti *et al.* (2008) described the same findings in the same cohort [in Italian].

Ferrante *et al.* (2007) examined cancer mortality in a cohort consisting of family members of men who had been employed in the asbestos-cement factory in Casale Monferrato, Italy, described in the preceding paragraph. Exposure was to a mix of crocidolite and chrysotile. Among women with domestic exposure to asbestos, 11 deaths from ovarian cancer were observed versus 7.7 expected (SMR, 1.42; 95%CI: 0.71–2.54).

Germani *et al.* (1999) examined mortality from ovarian cancer in a cohort of 631 women workers in Italy who had been compensated for asbestosis. The type of fibre to which the women were exposed was not specified. In the total cohort, there were nine deaths from ovarian cancer (SMR, 4.77; 95%CI: 2.18–9.06). In the subset of women from the asbestos-textile industry, there were four deaths from ovarian cancer (SMR, 5.26; 95%CI: 1.43–13.47). In the subcohort from the asbestos cement industry, there were five deaths from ovarian cancer (SMR = 5.40; 95%CI: 1.75 – 12.61).

Rösler *et al.* (1994) examined cancer mortality in a cohort of 616 women workers in Germany who had been occupationally exposed to asbestos. Proportionate mortality was computed according to cause of death. A total of 95% of the asbestos used in Germany at this time was chrysotile, but the authors state that "admixture of crocidolite cannot be excluded, particularly in the manufacture of asbestos textile." Two deaths

from ovarian cancer were observed versus 1.8 expected (SMR, 1.09; 95%CI: 0.13–3.95).

(i) Population-based cohort studies

Vasama-Neuvonen *et al.* (1999) conducted a case–control study of ovarian cancer of occupational exposures in Finland. The asbestos fibre type was not specified and the standardized incidence ratio was 1.30 (95%CI: 0.9–1.80) between ovarian cancer and exposure to "high levels of asbestos."

Pukkala *et al.* (2009) examined the incidence of ovarian cancer among women employed in various occupational categories in Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). Among the groups examined were plumbers, a group with known occupational exposure to asbestos. Fibre type was not specified. A total of four ovarian cancers were observed in these women plumbers. The standardized incidence ratio was 3.33 (95%CI: 0.91–8.52)

(b) Case–control studies

Langseth & Kjærheim (2004) conducted a nested case–control study to examine the association between asbestos exposure and ovarian cancer within a cohort of female pulp and paper workers in Norway that had previously been found to have excess mortality from ovarian cancer (37 ovarian cancers observed versus 24 expected; SIR, 1.50; 95%CI: 1.07–2.09). The asbestos fibre type was not specified. In the case–control study, the odds ratio for occupational exposure to asbestos, based on 46 cases of ovarian cancer, was 2.02 (95%CI: 0.72–5.66).

2.5 Synthesis

The Working Group noted that a causal association between exposure to asbestos and cancer of the larynx was clearly established, based on the fairly consistent findings of both the occupational cohort studies as well as the case-controlcase–control studies, plus the evidence for positive exposure–response relationships between cumulative asbestos exposure and laryngeal cancer-cancer of the larynx reported in several of the well-conducted cohort studies. This conclusion was further supported by the meta-analyses of 29 cohort studies encompassing 35 populations and of 15 case-controlcase–control studies of asbestos exposure and laryngeal cancercancer of the larynx undertaken by the IOM (2006). However, there is insufficient information in the published literature to discern whether any differences exist among asbestos fibre types in their ability to cause laryngeal cancercancer of the larynx.

The Working Group noted that a causal association between exposure to asbestos and cancer of the ovary was clearly established, based on five strongly positive cohort mortality studies of women with heavy occupational exposure to asbestos (Acheson *et al.*, 1982; Wignall & Fox, 1982; Germani *et al.*, 1999; Berry *et al.*, 2000; Magnani *et al.*, 2008). The conclusion received additional support from studies showing that women and girls with environmental, but not occupational exposure to asbestos (Ferrante *et al.*, 2007; Reid *et al.*, 2008, 2009) had positive, though non-significant, increases in both ovarian cancer incidence and mortality.

The Working Group carefully considered the possibility that cases of peritoneal mesothelioma may have been misdiagnosed as ovarian cancer, and that these contributed to observed excesses. Contravening that possibility is the finding that three of the studies cited here specifically examined the possibility that there were misdiagnosed cases of peritoneal mesothelioma, and all failed to find sufficient numbers of misclassified cases. The Working Group noted that the possibility of diagnostic misclassification had probably diminished in recent years because of the development of new immunohistochemical diagnostic techniques.

The conclusion of the Working Group received modest support from the findings of

non-significant associations between asbestos exposure and ovarian cancer in two case–control studies (Vasama-Neuvonen *et al.*, 1999; Langseth & Kjærheim, 2004).

And lastly, the finding is consistent with laboratory studies documenting that asbestos can accumulate in the ovaries of women with household exposure to asbestos (Heller *et al.*, 1996) or with occupational exposure to asbestos (Langseth *et al.*, 2007).

The study by Heller *et al.* (1996) was a histopathological study of ovaries from 13 women who had household contact with men who had documented exposure to asbestos, and of 17 women who gave no history of potential for asbestos exposure. The study found "significant asbestos fibre burdens" in the ovaries of nine (60.2%) of the exposed women and in only six (35%) of the unexposed women. Three of the exposed women had asbestos fibre counts in ovarian tissue of over 1 million fibres per gram (wet weight). By contrast, only one of the 17 women without household exposure had counts in that range.

The study by Langseth *et al.* (2007) found approximately 3–4 × 105 asbestos fibres per gram (net weight) in normal ovarian tissue taken from 2/46 patients with ovarian adenocarcinoma. It is unclear how many of these fibres were verified as asbestos because it is stated in the publication that three chrysotile and one crocidolite asbestos fibres were identified in Case 1, and two anthophyllite and one chrysotile fibre were identified in Case 2. This small number of confirmed asbestos fibres in only two of the patients could be due to sample contamination. Technical caveats associated with quantification of asbestos fibre tissue burdens are discussed in Section 4 of this *Monograph* and in IOM (2006).

Further discussion of the biological plausibility of an association between asbestos exposure and ovarian cancer is to be found in Section 4 of this *Monograph*.

The Working Group noted a positive association between exposure to abestos and cancer of the pharynx, based on the fairly consistent positive findings in a series of well conducted cohort studies of populations occupationally exposed to asbestos (Selikoff & Seidman, 1991; Sluis-Cremer *et al.*, 1992; Reid *et al.*, 2004; Pira *et al.*, 2005) as well as on the positive findings of three case–control studies (Zheng *et al.*, 1992; Marchand *et al.*, 2000; Berrino *et al.*, 2003). This conclusion was further supported by the findings of the meta-analysis conducted by the IOM. While tobacco smoking and alcohol consumption are clearly the dominant risk factors for cancer of the pharynx in industrialized countries, these associations between cancer of the pharynx and asbestos remained evident in several studies when tobacco and alcohol exposures were considered. The Working Group observed that the strongest associations between asbestos exposure and cancer of the pharynx were seen in studies that specifically examined cancer of the hypopharynx, the portion of the pharynx that is located closest to the larynx. However, there is insufficient information in the published literature to discern whether there are any differences among asbestos fibre types in their ability to cause cancer of the pharynx.

The Working Group noted a positive association between exposure to abestos and cancer of the stomach, based on the positive associations between asbestos exposure and death from stomach cancer observed in several of the cohort studies with heaviest asbestos exposure (Selikoff *et al.*, 1964; Enterline *et al.*, 1987; Raffn *et al.*, 1989; Liddell *et al.*, 1997; Musk *et al.*, 2008). The conclusion was further supported by the positive dose–response relationships observed between cumulative asbestos exposure and stomach cancer mortality in several cohort studies (Selikoff & Hammond., 1979; Zhang & Wang, 1984; Liddell *et al.*, 1997; Pang *et al.*, 1997). It was supported by the results of two large and well performed meta-analyses (Frumkin & Berlin, 1988; Gamble, 2008). It received borderline support from the IOM meta-analysis of cohort

studies, and also from the IOM meta-analysis of case–control studies, which show an especially strong relationship when only extreme exposures are considered. It was supported by the comparison developed by the Working Group between standardized incidence ratios for lung cancer and stomach cancer.

Positive associations between asbestos exposure and stomach cancer and positive dose–response relationships are most likely to be seen in studies of populations with prolonged heavy exposure to asbestos that had long-term follow-up, and that incorporated high-quality assessments of exposure. The less detailed assessments of exposure found in many of the published studies would have tended to bias study results towards the null, and thus impede recognition of an association between asbestos exposure and stomach cancer, even if such an association were truly present.

[The Working Group noted that heavy occupational exposure to dust, as had likely occurred in the case of the Quebec asbestos cohort, could have been an effect modifier. Low socioeconomic status is also a potential confounder.]

However, there was insufficient information in the published literature to discern whether any differences exist among asbestos fibre types in their ability to cause stomach cancer. In the study by Liddell *et al.* (1997) exposure was to virtually pure chrysotile asbestos, in the study by Musk *et al.* (2008) the exposure was predominantly to crocidolite, and in most of the other published studies that observed positive associations, populations were exposed to mixtures of different asbestos fibres.

The Working Group noted a positive association between exposure to abestos and cancer of the colorectum, based on the fairly consistent findings of the occupational cohort studies, plus the evidence for positive exposure–response relationships between cumulative asbestos exposure and cancer of the colorectum consistently reported in the more detailed cohort studies (McDonald *et al.*, 1980; Albin *et al.*, 1990; Berry *et al.*, 2000; Aliyu *et al.*, 2005). The conclusion was further supported by the results of four large and well performed meta-analyses (Frumkin & Berlin 1988; Homa *et al.*, 1994; IOM, 2006; Gamble, 2008).

Positive exposure–response relationships between asbestos exposure and cancer of the colorectum appear most likely to be seen in studies of populations with prolonged heavy exposure to asbestos that had long-term follow-up, and that incorporated high-quality assessments of exposure. The less detailed assessments of exposure found in many of the published studies would have tended to bias study results towards the null, and thus impede recognition of an association between asbestos exposure and cancer of the colorectum, even if such an association were truly present.

The apparently non-positive findings of several the case–control studies are not a deterrent to this conclusion. The majority of these case–control studies incorporated relatively little information on levels of asbestos exposure; indeed, most of them considered exposure as simply a dichotomous yes/no variable. Some of the case–control studies also may be compromised by inadequate duration of follow-up. Thus, the Garabrant study (Garabrant *et al.*, 1992) may be subject to the criticism, offered by Gerhardsson de Verdier *et al.* (1992) that “the highest duration of exposure…was ‘at least 15 years,’ a period that may be too short to detect an elevated risk.”

There is some suggestion in the literature that the association between asbestos might be stronger for colon cancer than for rectal cancer. This view is supported by the meta-analysis of Gamble (2008) which found a positive dose–response relationship for cancer of the colorectum taken together, but not for rectal cancer. It is supported also by the study of Jakobsson *et al.* (1994), which found excess of cancer of the right colon in asbestos-exposed workers, but not of the left colon.

However, there was insufficient information in the published literature to discern whether any differences exist among asbestos fibre types in their ability to cause cancer of the colorectum. It is of note in the study by McDonald *et al.* (1980) that exposure was to virtually pure chrysotile asbestos, whereas in most of the other studies cited above, populations were exposed to mixtures of different asbestos fibres.

3. Cancer in Experimental Animals

3.1 Introduction

Asbestos is a collective name for six different types of fibres: chrysotile, crocidolite, amosite, anthophyllite, tremolite, actinolite (see Section 1). Dusts from various deposits of the same type of asbestos can cause variations in the severity of the effects observed. Erionite is a fibrous zeolite found in Central Anatolia (Turkey), and Oregon (USA) (see Section 1 of the *Monograph* on Erionite). Talc is a hydrated magnesium silicate, and talc ore may contain several other minerals including anthophyllite, tremolite, calcite, dolomite, magnesite, antigorite, quartz, pyrophyllite micas, or chlorites (see Section 1).

The definition of pathogenic fibre properties as "sufficiently long, thin, and durable" is the subject of much debate, as are the differences between the exposure–response relationships or retained dose–response relationships of asbestos fibres in man and in rats, and the potential differences in the carcinogenicity of chrysotile compared to the various amphibole asbestos types. One of the reasons for a potential difference is a difference in the biopersistence between the two asbestos groups mentioned. The biopersistence is higher in the amphibole group (Hesterberg *et al.*, 1996, 1998a, b). The rat is the main test model for fibre-induced diseases. As the removal of asbestos fibres due to biosolubility is slow compared to the lifetime of rats and hamsters, experiments with this model may not be appropriate in predicting results of risk in humans (Berry, 1999).

Critical fibre dimensions to be used in toxicology and occupational regulations were discussed by the Working Group. It is generally agreed that the carcinogenic potency of a fibre increases with fibre length. Apart from the ongoing scientific view, standards of regulated fibres, with few exceptions, are based on the WHO fibre definition: aspect ratio ≥ 3: 1, length ≥ 5 µm, diameter ≤ 3 µm.

The tested materials (asbestos and erionite) are not presented in separate tables as in many cases they were tested in parallel experiments. The reason to split the inhalation studies into two tables (Table 3.1; Table 3.2) is that in many studies, various asbestos fibres were used as positive control in studies in which man-made fibres were tested (Table 3.2). In these latter studies, normally only one asbestos concentration was used. As for intrapleural and intraperitoneal studies, Table 3.4 is separate from Table 3.5 because the studies of Stanton *et al.* (1981) (see Table 3.5) included many fibre types – which also included fibres not to be reviewed here – and was designed to investigate the effect of fibre length and fibre type on mesothelioma induction.

A general evaluation on the type of fibre application in animal studies and an evaluation of some of the asbestos studies listed in Tables 3.1–3.5 can be found in Pott (1993) and IARC (2002).

3.2 Inhalation exposure

Table 3.1 and Table 3.2 give an overview of the numerous inhalation experiments on asbestos, and a few experiments on erionite. Some of these are described more extensively below.

Bronchial carcinomas and pleural mesotheliomas have been observed in rats after exposure to chrysotile, crocidolite, amosite, anthophyllite, and tremolite fibres. In these studies, there was no consistent increase in

tumour incidence at other sites. [The Working Group noted that in many studies, no complete histopathology was done.] All relatively short UICC asbestos preparations showed chronic effects in lung (based on fibre lenghts > 5 µm in the dust chamber) for fibres quantitatively roughly the same.

One of the first inhalation study with asbestos in rats that showed exposure–response relationships is the experiment of Wagner *et al.* (1974). Wistar rats were exposed to 10–15 mg/m³ of one of the five UICC standard asbestos samples for 7 hours per day, mostly 5 days per week. The duration of exposure lasted from one day to 24 months. According to the reported data, in the group exposed to crocidolite for one day, lung tumours and one mesothelioma were found in 7/43 rats (16%). The corresponding exposure to chrysotile A (from Canada) resulted in lung tumours in 5/45 rats; for amosite 4/45 rats developed lung tumours and one mesothelioma. Three months of exposure to the five UICC standard asbestos samples resulted in the following thoracic tumour (mainly of the lung) incidences: chrysotile A, 44%;chrysotile B (from Zimbabwe), 53%; crocidolite, 42%; amosite, 27%; anthophyllite, 16%. Further results are listed in Table 3.1. In the 126 control rats, seven animals were also found to have lung tumours (Table 3.3). This high spontaneous lung tumour rate is a unique finding in Wistar rats. A review of unexposed control groups of many other studies shows that spontaneous lung tumours are very rare in this rat strain (Pott *et al.*, 1995; Table 3.3); on average, the incidence is less than one percent. Therefore, the very high tumour incidences described in this first inhalation study of Wagner *et al.* (1974) might be a misinterpretation of histopathological lesions because of a lack of experience at that time.

In a study conducted by Davis *et al.* (1978), five groups of Wistar rats were exposed to chrysotile (2.0, 10 mg/m³), crocidolite (5.0, 10 mg/m³), or amosite (10 mg/m³). The highest tumour incidences (21–38%) were found in the chrysotile-exposed animals. This may be due to the relatively high fraction of fibres longer than 20 µm in the chrysotile dust used in this experiment. In addition to the lung tumours, extrapulmonary neoplasms included a relatively large number of peritoneal connective tissue tumours.

In a further study by Davis *et al.* (1986b), inhalation of short-fibred amosite did not produce tumours in Wistar rats (0/42). In contrast, there was a tumour incidence of 13/40 (33%) in a group exposed to long-fibred amosite. [The Working Group noted that extensive milling to produce short fibres may have altered the surface reactivity, see Section 4].

A group of 48 SPF Fischer rats was exposed to 10 mg/m³ UICC chrysotile B by inhalation for 7 hours per day, 5 days per week, for 12 months (Wagner *et al.*, 1984b). This group served as positive controls in a study in which various man-made fibres were tested. After exposure, the animals were kept until natural death. Twelve thoracic tumours (one adenoma, 11 adenocarcinomas) were observed in 48 rats. In the untreated control group, no lung tumours were observed in 48 rats.

Smith *et al.* (1987) exposed groups of 58 female Osborne-Mendel rats to 7 mg/m³ UICC crocidolite asbestos for 6 hours per day, for 5 days per week, for 2 years. After this treatment, rats were observed for life. The tumour incidence in rats exposed to crocidolite was 3/57 (one mesothelioma and two carcinomas). In the control group, no tumours were observed in 184 rats.

Special attention should be drawn to the crocidolite study with male Fischer rats of McConnell *et al.* (1994) because this study is very well documented. The exposure to 10 mg dust/m³ (with 1610 WHO fibres/mL containing 236 fibres > 20 µm) for 6 h per day, 5 days per week had to be stopped after 10 months because of unexpected mortality, which was interpreted as a sign that the maximum tolerated dose had been exceeded. The number of WHO fibres per µg dry

Table 3.1 Studies of cancer in experimental animals exposed to various asbestos species and erionite (inhalation exposure)[a]

Test substance	Concentration (mg/m³)	Aerosol fibres per mL (L > 5 μm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/No. of animals examined	% tumours	Comments	Reference
Asbestos									
Chrysotile, Canada	86	NR	White rats 16 months or longer	6 h/d 5 d/wk 62 wk	0	10/41[c]	24		Gross et al. (1967)
Crocidolite	50	1105	Sprague-Dawley rats lifetime	4 h/d 4 d/w 24 mo	0	5/46	11		Reeves et al. (1974)
Chrysotile UICC/A	14.7	NR	Wistar rats lifetime	7 h/d 1 d	0	5/45	11		Wagner et al. (1974)
	12.3	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	16/36	44		
	10.7	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	8/19	42		
	10.9	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	19/27	70		
	10.1	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	0	11/17	65		

Table 3.1 (continued)

Test substance	Concentration (mg/m³)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile UICC/B	9.7	NR	Wistar rats lifetime	7 h/d 1 d	0	1/42	2		
	12.1	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	18/34	53		
	10.2	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	5/17	29		
	10.7	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	3	14/23	61		
	10.1	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	1	11/21	52		
Crocidolite UICC	12.5	NR	Wistar rats lifetime	7 h/d 1 d	1	7/43	16		
	12.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	1	15/36	42		
	10.7	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	4/18	22		
	10.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	20/26	77		
	10.3	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	0	13/18	72		

Table 3.1 (continued)

Test substance	Concentration (mg/m³)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Amosite UICC	14.1	NR	Wistar rats lifetime	7 h/d 1 d	1	4/45	9		
	12.4	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	10/37	27		
	11.2	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	2/18	11		
	10.8	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	10/25	40		
	10.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	0	13/21	62		
Anthophyllite UICC	12.8	NR	Wistar rats lifetime	7 h/d 1 d	0	2/44	5		
	13.5	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	6/37	16		
	10.9	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	6/18	33		
	11.4	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	21/28	75		
	10.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	1	17/18	94		
Amosite UICC	10	550	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	2/43	5		Davis et al. (1978)

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Crocidolite UICC	5	430	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	3/43	7		
	10	860	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	1/40	3		
Chrysotile SFA	10.8	430	Wistar rats lifetime	7.5 h/d 5 d/wk 3 mo	1	1/40	3		Wagner et al. (1980)
	10.8	430	Wistar rats lifetime	7.5 h/d 5 d/wk 6 mo	0	4/18	22		
	10.8	430	Wistar rats lifetime	7.5 h/d 5 d/wk 12 mo	0	8/22	36		
Chrysotile grade 7	10.8	1020	Wistar rats lifetime	7.5 h/d 5 d/wk 3 mo	0	1/39	3		
	10.8	1020	Wistar rats lifetime	7.5 h/d 5 d/wk 6 mo	0	5/18	28		
	10.8	1020	Wistar rats lifetime	7.5 h/d 5 d/wk 12 mo	0	3/24	13		
Chrysotile UICC (/B)	10.8	3750	Wistar rats lifetime	7.5 h/d 5 d/wk 3 mo	0	4/40	10		
	10.8	3750	Wistar rats lifetime	7.5 h/d 5 d/wk 6 mo	0	10/18	56		
	10.8	3750	Wistar rats lifetime	7.5 h/d 5 d/wk 12 mo	0	6/23	26		

Table 3.1 (continued)

Test substance	Concentration (mg/m³)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile UICC /A	2	390	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	9/42	21		Davis et al. (1978)
Chrysotile UICC /A	10	1950	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	15/40	38		
Chrysotile UICC	9	NR	Wistar rats lifetime	7 h/d 1 d/wk 12 mo	0	6/43	14	Peak dosing (one d/wk); no control group	Davis et al. (1980a)
Amosite UICC	50	NR	Wistar rats lifetime	7 h/d 1 d/w 12 mo	0	6/44	14	Peak dosing (one d/wk); no control group	
Chrysotile UICC	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	15/43 (8 malignant, 7 benign)	35	No control group	Davis et al. (1980b)
Chrysotile "factory"	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	11/42 (3 maligant, 8 benign)	26	No control group	
Amosite "factory"	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	0/37	0	No control group	
Amosite UICC	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	2/40	5	No control group	
Tremolite	10	1600	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	20/39	51		Davis et al. (1985)
Crocidolite UICC	10	1630/350[d]	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	0	1/28	4		Wagner et al. (1985)
Chrysotile WDC textile yarn	3.5	679	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	18/41	44		Davis et al. (1986a)

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile factory WDC	3.7	468	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	21/44	48		
Chrysotile textile yarn	3.5	428	Wistar rats lifetime	7 h/d 5 /wk 12 mo	1	16/42	38		
Chrysotile experimental WDC	3.5	108	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	4	21/43	49		
Chrysotile experimental WDC reversed daylight	3.8	111	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	18/37	49		
Amosite "long"	10	2060/1110[d]	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	13/40	33		Davis et al. (1986b)
Amosite "short"	10	70/12[d]	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	0/42	0		
Crocidolite UICC	10	NR	Fischer rats lifetime	6 h/d 5 d/wk 12 mo	0	1/28	4		Wagner et al. (1987)
Chrysotile, Canada, "long"	10	5510/1930[d]	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	22/40	55	1 peritoneal mesothelioma was observed in addition	Davis & Jones (1988)
Chrysotile, Canada, "short"	10	1170/330[d]	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	7/40	18	1 peritoneal mesothelioma was observed in addition	
Chrysotile UICC/A "discharged"	10	2670	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	11/39	28		Davis et al. (1988)

Table 3.1 (continued)

Test substance	Concentration (mg/m³)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile UICC/A	10	2560	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	14/36	39		
Chrysotile UICC /A	10	2560	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	13/37	35		Davis et al. (1991a)
Chrysotile UICC /A	10	2545	Wistar rats lifetime	5 h/d 5 d/w 12 mo	2	26/41	63	Increase of tumour rate by particulate dust	
+ titanium dioxide	+ 10	-		+ 2 h/d 5 d/w 12 mo					
Chrysotile UICC /A	10	1960	Wistar rats lifetime	5 h/d 5 d/w 12 mo	6	22/38	58	Increase of tumour rate by particulate dust	
+ quartz S600	+ 2	-		+ 2 h/d 5 d/w 12 mo					
Amosite "long"	10	3648	Wistar rats lifetime	5 h/d 5 d/w 12 mo	2	20/40	50	Increase of tumour rate by particulate dust	Davis et al. (1991a)
+ titanium dioxide	+ 10	-		+ 2 h/d 5 d/w 12 mo					
Amosite "long"	10	4150	Wistar rats lifetime	5 h/d 5 d/w 12 mo	8	26/39	67	Increase of tumour rate by particulate dust	
+ quartz S600	+ 2	-		+ 2 h/d 5 d/w 12 mo					
Chrysotile Jeffrey	11	NR	Fischer rats lifetime	6 h/d 5 d/wk 12 mo	0	20/52	38		Mc Connell et al. (1991)

Table 3.1 (continued)

Test substance	Concentration (mg/m³)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile	NR	NR	Baboons 6 yr	6 h/d 5 d/wk 4 years	0	0/6[e]	0		Goldstein & Coetzee (1990)
Crocidolite UICC	12-14	1130-1400	Baboons 6 yr	6 h/d 5 d/wk 4 yr	3	3/21[f]	14		
Amosite UICC	7	1110	Baboons 6 yr	6 h/d 5 d/wk 4 yr	2	2/11[f]	18		Goldstein & Coetzee (1990), Webster et al. (1993)
Erionite									
Erionite, Oregon	10	354	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	27	27/28	96		Wagner et al. (1985)
Erionite, Oregon	NR	NR	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	24	24/27	89	No control group	Wagner (1990)
Erionite, Oregon "short"	NR	NR	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	0	0/24	0	No control group	

[a] negative control groups: seeTable 3.3
[b] Animals with benign or malignant lung tumour or pleural mesothelioma. The percentage of animals with tumours is related to the number of rats examined which were alive at a certain point in time (e.g. at the beginning of the experiment or after one year, or at the point in time of the death of the first animal with a tumour). Often, this is not clearly specified.
[c] observation time ≥6 mo
[d] Fibre count refers to fibres with lengths > 10 µm and diameters < 1 µm, in the aerosol
[e] observation time ≥4 yr
[f] observation time ≥5 yr
d, day or days; h, hour or hours; mo, month or months; NR, not reported; wk, week or weeks; yr, year or years
From Pott & Roller (1993b)

Table 3.2 Studies of cancer in experimental animals in which asbestos was used as positive control group (in inhalation studies of various man-made mineral fibres)

Test substance	Concentration (mg/m^3)	Aerosol fibres per cm^3 (L > 5 µm)	Species and strain (No. at risk); Observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[a] / No. of animals	% tumours	Comments	Reference
Amosite	NR	981 89 f > 20 µm/cm^3	AF/HAN rats, 24 mo	7 h/d 5 d/wk 12 mo	2	18/42 (7 carcinomas, 9 adenomas)	43		Davis et al. (1996), Cullen et al. (2000)
Chrysotile UICC/B	10	NR	Fischer rats, lifetime	7 h/d 5 d/wk 12 mo	0	11/56 (7 adenocarcinomas, 4 adenomas)	20		McConnell et al. (1984)
Chrysotile UICC/B	10	3832/1513[b]	Fischer rats, lifetime	7 h/d 5 d/wk 12 mo	0	12/48 (11 adenocarcinomas, 1 adenoma)	25		Wagner et al. (1984b)
Chrysotile NIEHS, Canada	10	10 600	Fischer rats, 24 mo	6 h/d 5 d/wk 24 mo	1	14/69	20		Hesterberg et al. (1993)
Crocidolite	10	1610	Fischer 344/N rats, 24 mo	6 h/d 5 d/wk 10 mo	1	14/106 (10 adenomas, 5 carcinomas)	13		McConnell et al. (1994)
Crocidolite UICC	7	3000/90[b]	Osborne-Mendel rats, lifetime	6 h/d 5 d/wk 24 mo	1	3/57 (1 mesothelioma, 2 carcinomas)	5		Smith et al. (1987)
Chrysotile UICC/A	Cumulative dose: 13 800 mg.h/m^3	NR	Rats, lifetime	6 h/d 5 d/wk 18 mo	0	9/39 (5 adenomas, 1 adenocarcinoma, 3 squamous cell carcinomas)	23	Strain not specified	Pigott & Ishmael (1982)
Amosite UICC	300	3090	Sprague-Dawley rats, 18–24 mo	6 h/d 5 d/wk 3 mo	0	3/16[c]	19	Small number of animals; D= 0.4 µm	Lee et al. (1981), Lee & Reinhardt (1984)
Chrysotile, Canada	5	5901	Wistar rats, 24 mo	5 h/d 5 d/wk 12–24 mo	0	9/47	19		Le Bouffant et al. (1987)
Chrysotile Calidria	6	131	Wistar rats, 24 mo	5 h/d 4 d/wk 12 mo	0	0/50	0		Muhle et al. (1987)

Table 3.2 (continued)

Test substance	Concentration (mg/m³)	Aerosol fibres per cm³ (L > 5 µm)	Species and strain (No. at risk); Observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[a] / No. of animals	% tumours	Comments	Reference
Crocidolite, South Africa	2.2	162	Wistar rats, 24 mo	5 h/d 4 d/wk 12 mo	0	1/50	2		Muhle et al. (1987)
Amosite UICC	300	3090	Syrian golden hamsters, 18–24 mo	6 h/d 5 d/wk 3 mo	0	0/12	0	Small number of animals diameter, 0.4 µm	Lee et al. (1981), Lee & Reinhardt (1984)
Crocidolite UICC	7	3000/90[b]	Syrian golden hamsters, lifetime	6 h/d 5 d/wk 24 mo	0	0/58	0		Smith et al. (1987)
Amosite	0.8	36 WHO f/cm³ 10 f> 20 µm/cm³	Syrian golden hamsters, 84 wk	6 h/d 5 d/wk 78 wk	3	3/83	3.6		McConnell et al. (1999)
	3.7	165 WHO f/cm³ 38 f> 20 µm/cm³	Syrian golden hamsters, 84 wk	6 h/d 5 d/wk 78 wk	22	22/85	26		
	7.1	263 WHO f/cm³ 69 f> 20 µm/cm³	Syrian golden hamsters, 84 wk	6 h/d 5 d/wk 78 wk	17	17/87	20		
Crocidolite UICC	13.5	1128	Baboons lifetime	7 h/d 5 d/wk 40 mo	0	0/10	0	All males	Goldstein et al. (1983)

[a] n = animals with benign or malignant lung tumour or pleural mesothelioma
[b] Number of fibres with a length > 10 µm and a diameter < 1 µm in the aerosol
d, day or days; f, fibre; h, hour or hours; mo, month or months; NR, not reported; RCF, refractory ceramic fibre; wk, week or weeks
From Pott & Roller (1993b)

Table 3.3 Negative controls (clean air for lifetime) in carcinogenicity studies after inhalation exposures from Table 3.1 and Table 3.2

Species and strain	Number of pleural mesothelioma	No. of animals with thoracic tumours[a]/ No. of animals	Reference
Fischer rats	0	0/48	Wagner et al (1984b)
Fischer rats	0	0/28	Wagner et al. (1985)
Fischer rats	0	0/28	Wagner et al. (1987)
Fischer rats	0	1/56	McConnell et al. (1991)
Fischer rats	0	4/123	Hesterberg et al. (1993)
Fischer rats	0	2/126	McConnell et al. (1994)
Osborne-Mendel rats	0	0/184	Smith et al. (1987)
Sprague-Dawley rats	0	1/5	Reeves et al. (1974)
Sprague-Dawley rats	0	0/19	Lee et al. (1981)
White rats	0	0/25	Gross et al. (1967)
Wistar rats	0	7/126	Wagner et al. (1974)
Wistar rats	0	0/20	Davis et al. (1978)
Wistar rats	0	1/71	Wagner et al. (1980)
Wistar rats	0	0/36	Davis et al. (1985)
Wistar rats	0	2/39	Davis et al. (1986a)
Wistar rats	0	0/25	Davis et al. (1986a)
Wistar rats	0	0/110	Muhle et al. (1987)
Wistar rats	0	2/36	Davis et al. (1988)
Wistar rats	0	0/25	Davis et al. (1988)
Wistar rats	0	2/47	Davis & Jones (1988)
Wistar rats	0	2/47	Davis et al. (1991a)
Syrian golden hamsters	0	1/170	Smith et al. (1987)
Syrian golden hamsters	0	0/83	Mc Connell et al. (1999)

[a] *n* = animals with benign or malignant lung tumour or pleural mesothelioma

lung tissue was 1850 (73 fibres > 20 μm) at the end of exposure and 759 WHO fibres (41 fibres > 20 μm) 12 months later. Fourteen out of 106 rats (13.2%), which survived the second year or longer, died with lung tumour (five of these rats developed lung carcinomas), and one rat also developed a mesothelioma. In the control group, 2/126 rats developed lung adenomas.

In two lifetime studies, male and female Fischer rats were exposed to either 10 mg/m^3 erionite (Wagner *et al.*, 1985) or an unknown concentration of erionite (Wagner, 1990) for 6 hours per day, 5 days per week, for 12 months. Twenty seven out of 28 rats, and 24/27 rats developed pleural mesotheliomas, respectively. No lung tumours were observed. [The Working Group noted the lack of control group in the study by Wagner (1990).]

McConnell *et al.* (1999) exposed three groups of 125 male Syrian golden hamsters to 0.8, 3.7 and 7.1 mg/m^3 amosite for 6 hours per day, 5 days per week, for 78 weeks. They were then held unexposed for 6 weeks. Among animals that survived for at least 32 weeks, 3/83, 22/85 and 17/87 developed pleural mesotheliomas, respectively. No mesotheliomas were observed in 83 untreated controls and no lung tumours were observed in any groups.

Some experiments were reported with baboons. After amosite exposure and crocidolite exposure for 4 years, 2/11 baboons and 3/21 baboons developed pleural mesothelioma,

respectively (Goldstein & Coetzee, 1990; Webster *et al.*, 1993).

3.3 Intrapleural and intraperitoneal administration

Animal experiments had shown that an intrapleural injection of a suspension of asbestos dusts in rats leads to mesotheliomas (Wagner, 1962; Wagner & Berry, 1969). The serosa has subsequently been taken as a model for the examination of the carcinogenicity of fibrous dusts in numerous studies. Some groups have opted for administration into the pleural cavity, others preferring intraperitoneal injection of dust suspensions. In comparison with the intrapleural model, the intraperitoneal carcinogenicity test on fibres has proven to be the method with the far greater capacity and, consequently, the greater sensitivity (see also Pott & Roller, 1993a). Results from these numerous experiments using asbestos and erionite are listed in Table 3.4.

Table 3.5 contains a summary of the experiments by Stanton *et al.* (1981). In this extensive study, the authors implanted 72 dusts containing fibres of various sizes in the pleura of Osborne-Mendel rats. The probability of the development of pleural mesotheliomas was highest for fibres with a diameter of less than 0.25 µm and lengths greater than 8 µm.

In summary, samples of all six asbestos types and of erionite were administered to rats by intrapleural or intraperitoneal injection in numerous studies. Consistently, mesothelima induction was observed when samples contained a sufficient fibre number with a fibre length > 5 µm.

3.4 Intratracheal administration

Only a few studies have been carried out with intratracheal instillation of asbestos fibres in rats (Pott *et al.*, 1987; Smith *et al.*, 1987), and hamsters (Pott *et al.*, 1984; Feron *et al.*, 1985; Smith *et al.*, 1987). Principally, in this experimental model, asbestos fibres induced lung tumours in rats, and lung tumours and mesotheliomas in hamsters. Studies in hamsters are described below.

In a 2-year study, a group of male Syrian golden hamsters [initial number unspecified] was intratracheally instilled with 1 mg UICC crocidolite in 0.15 mL saline once a week for 8 weeks. At the end of the experiment, the incidences of lung carcinomas and of pleural mesotheliomas were 9/142 [$P < 0.01$] and 8/142 [$P < 0.01$], respectively. No thoracic tumours were observed in 135 titanium-dioxide-treated control animals (Pott *et al.*, 1984).

In a lifetime study, a group of Syrian golden hamsters [sex and initial number unspecified] was intratracheally instilled with 2 mg UICC crocidolite in 0.2 mL saline once a week for 5 weeks. At the end of the experiment, 20/27 animals developed broncho-alveolar tumours ($p<0.05$), including 7/27 with malignant tumours [$p<0.05$]. No broncho-alveolar tumours were observed in 24 saline-treated controls (Smith *et al.*, 1987).

3.5 Oral administration

A study on the carcinogenicity of ingested asbestos fibres involved male F344 rats groups exposed to amosite or chrysotile in combination with subcutaneous administration of a known intestinal carcinogen, azoxymethane (10 weekly injections of 7.4 mg/kg body weight). Fibres were administered three times a week for 10 weeks by intragastric bolus dosing (10 mg in 1 mL saline). The first experiment in this study included a full set of appropriate control groups. The experiment was terminated at 34 weeks. Neither amosite nor UICC chrysotile B, in combination with azoxymethane, increased the incidence of any intestinal tumours (≈10%) above that produced by azoxymethane alone, but the combination with either fibre type produced 4–5-fold increases

(not significant, $P > 0.1$) in metastatic intestinal tumours. A second experiment with larger groups, the same dosing regimen, and for lifetime, but with a more limited design, tested only amosite in combination with azoxymethane versus azoxymethane. Amosite did not enhance azoxymethane-induced intestinal tumours (incidence, 77% versus 67%) (Ward *et al.*, 1980; IOM, 2006). [The Working Group noted that the lack of untreated vehicle controls in the second experiment made interpretation of the results difficult considering that, compared to historical controls, there was a non-significant increase in intestinal tumours in rats exposed only to amosite (≈33%). One cannot know whether the results observed were associated with the asbestos or with irritation from the procedure, although one would not anticipate that gavage itself would impact the lower portion of the gastrointestinal tract.]

The most definitive animal studies of oral exposure to asbestos were a series of lifetime studies conducted by the National Toxicology Program (NTP, 1983, 1985, 1988, 1990a, b), in which asbestos (chrysotile, crocidolite, and amosite) was administered in the feed of rats and hamsters. Nonfibrous tremolite was also tested in rats according to the same protocol (NTP, 1990c). Exposure of dams of the study animals (1% in the diet) was followed by exposure of the pups by gavage (0.47 mg/g water) while they were nursing, and then in the diet for the remainder of their lives: they were exposed to asbestos at the level of 1%, which was estimated by the investigators to be about 70000 times the greatest possible human exposure in drinking-water. Histopathological examination of the entire colorectum was performed. No increases in the incidence of gastrointestinal lesions (inflammatory, preneoplastic, or neoplastic) were found after exposure to intermediate-length chrysotile (from Quebec) in hamsters, to short chrysotile (from New Idria) in rats or hamsters, to amosite in rats or hamsters, to crocidolite in rats, or to non-fibrous tremolite in rats. The mesentery was examined in detail, as well as mesenteric lymph nodes and sections of the larynx, trachea, and lungs from every animal. No lesions were found in any of those tissues. The only finding of note in the gastrointestinal tract was a slight increase in the incidence of adenomatous polyps in the large intestine after exposure to the intermediate-length chrysotile (from Quebec) in male rats (9/250 versus 0/85, $P = 0.08$), but preneoplastic changes in the epithelium were not found (NTP, 1985; IOM, 2006).

3.6 Intragastric administration

White rats, 2–3 months old, were surgically applied, on the greater curvature of the stomach, a perforated capsule containing 0 (control) or 100 mg chrysotile asbestos in a filler (beef fat: natural wax, 1:1). Tumours observed in 18/75 asbestos-exposed rats, between 18–30 months after the beginning of the experiment, were the following: eight gastric adenomas, two gastric adenocarcinomas, one gastric carcinoma, one cancer of the forestomach, one small intestine adenocarcinoma, two peritoneal mesotheliomas, and three abdominal lymphoreticular sarcomas. No tumours were observed in 75 control animals (Kogan *et al.*, 1987). [The Working Group noted various unresolved questions regarding the design of this study in particular the very high dose of 100 mg.]

3.7 Studies in companion animals

Mesotheliomas were reported in pet dogs with asbestos exposure in the households of their owners. Eighteen dogs diagnosed with mesothelioma and 32 age-, breed- and gender-matched control dogs were investigated. Sixteen owners of cases and all owners of controls were interviewed. An asbestos-related occupation or hobby of a household member was significantly associated with mesothelioma observed in cases (OR,

Table 3.4 Studies of cancer in rats exposed to asbestos fibres and erionite (intrapleural and intraperitoneal administration)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres [a] [10^9]	Tumour incidence [b]		Significance [c]	Comments
					n/z	%		
Asbestos	**Asbestos type**							
Wistar – Pott et al. (1989)	Actinolite	0.25	i.p.	0.1	20/36	56	***	
Wistar – Wagner et al. (1973)	Amosite UICC	20	i.pl.	NR	11/32	34	***	
Wistar – Davis et al. (1991b)	Amosite from UICC	0.01	i.p.	0.0003	4/48	8	*	
Wistar – Davis et al. (1991b)	Amosite from UICC	0.05	i.p.	0.002	8/32	25	***	
Wistar – Davis et al. (1991b)	Amosite from UICC	0.5	i.p.	0.02	15/32	47	***	
Wistar – Wagner et al. (1973)	Anthophyllite UICC	20	i.pl.	NR	8/32	25	***	
Wistar – Wagner et al. (1973)	Chrysotile UICC/A	20	i.pl.	NR	7/31	23	***	
Sprague-Dawley – Monchaux et al. (1981)	Chrysotile UICC/A	20	i.pl.	NR	14/33	42	***	
Sprague-Dawley – Wagner et al. (1984b)	Chrysotile UICC/A	20	i.pl.	19.6	6/48	13	**	
Wistar – Pigott & Ishmael (1992)	Chrysotile UICC/A	20	i.pl.	NR	7/48	15	***	
Fischer – Coffin et al. (1992)	Chrysotile UICC/A	0.5	i.pl.	0.90	118/142[d]	78	***[d]	
		2		3.6		87		
		4		7.2		92		
		8		14		83		
		16		29		83		
		32		57		75		
Wistar – Wagner et al. (1973)	Chrysotile UICC/B	20	i.pl.	NR	10/32	31	***	
Wistar – Wagner et al. (1980)	Chrysotile UICC/B	20	i.pl.	NR	5/48	10	*	
Fischer – Wagner et al. (1987)	Chrysotile UICC/B	20	i.pl.	NR	19/39	49	***	
Wistar – Pott et al. (1989)	Chrysotile UICC/B	0.25	i.p.	0.2	23/34	68	***	

Table 3.4 (continued)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres [a] [10^9]	Tumour incidence [b] n/z	%	Significance [c]	Comments
Wistar – Davis et al. (1991b)	Chrysotile from UICC/A	0.01	i.p.	0.002	2/48	4	NS	
Wistar – Davis et al. (1991b)	Chrysotile from UICC/A	0.05	i.p.	0.009	12/32	38	***	
Wistar – Davis et al. (1991b)	Chrysotile from UICC/A	0.5	i.p.	0.09	26/32	81	***	
Wistar – Wagner et al. (1973)	Crocidolite UICC	20	i.pl.	NR	19/32	59	***	
Fischer – Wagner et al. (1987)	Crocidolite UICC	20	i.pl.	NR	34/40	85	***	
Fischer – Wagner (1990)	Crocidolite UICC	20	i.pl.	NR	24/32	75	***	
Sprague-Dawley – Monchaux et al. (1981)	Crocidolite UICC	20	i.pl.	NR	21/39	54	***	
Osborne-Mendel – Stanton et al. (1981)	Crocidolite UICC	40	i.pl.	NR	14/29	48	***	
Fischer – Wagner et al. (1984a)	Crocidolite UICC	20	i.pl.	NR	35/41	85	***	
Fischer – Wagner et al. (1984a)	Crocidolite UICC ground 1 h	20	i.pl.	NR	34/42	81	***	
Fischer – Wagner et al. (1984a)	Crocidolite UICC ground 2 h	20	i.pl.	NR	34/42	81	***	
Fischer – Wagner et al. (1984a)	Crocidolite UICC ground 4 h	20	i.pl.	NR	15/41	37	***	
Fischer – Wagner et al. (1984a)	Crocidolite UICC ground 8 h	20	i.pl.	NR	13/42	31	***	
Fischer – Coffin et al. (1992)	Crocidolite UICC	0.5	i.pl.	0.04	65/144[d]	29	** [d]	
		2		0.16		13		
		4		0.32		50		
		8		0.65		67		
		16		1.3		58		
		32		2.6		54		
Wistar – Davis et al. (1991b)	Crocidolite from UICC	0.01	i.p.	0.0004	0/48	0	NS	
Wistar – Davis et al. (1991b)	Crocidolite from UICC	0.05	i.p.	0.002	8/32	25	***	

Table 3.4 (continued)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres [a] [10^9]	Tumour incidence [b] n/z	Tumour incidence [b] %	Significance [c]	Comments
Wistar – Davis et al. (1991b)	Crocidolite from UICC	0.5	i.p.	0.02	10/32	31	***	
Wistar – Pott et al. (1987)	Crocidolite South Africa	0.5	i.p.	0.05	18/32	56	***	
Wistar – Roller et al. (1996)	Crocidolite A	0.5	i.p.	0.042	25/32	78	***	All females
Wistar – Roller et al. (1996)	Crocidolite A	0.5	i.p.	0.042	32/48	67	***	All females
Wistar – Roller et al. (1996)	Crocidolite C	0.5	i.p.	0.042	20/39	51	***	
Wistar – Davis et al. (1985)	Tremolite, Korea	25	i.p.	NR	27/29	93	***	
Wistar – Roller et al. (1996)	Tremolite B	3.3	i.p.	0.057	9/40	23	***	
Wistar – Roller et al. (1996)	Tremolite B	15	i.p.	0.26	30/40	75	***	
Erionite	Erionite type							
Sprague-Dawley – Pott et al. (1987)	Karain	1.25	i.p.	NR	38/53	72	***	
Sprague-Dawley – Pott et al. (1987)	Karain	5	i.p.	NR	43/53	81	***	
Sprague-Dawley – Pott et al. (1987)	Karain	20	i.p.	G	37/53	70	***	
Fischer – Wagner et al. (1985)	Karain	20	i.pl.	NR	38/40	95	***	
Fischer – Wagner et al. (1985)	Oregon	20	i.pl.	NR	40/40	100	***	
Wistar – Pott et al. (1987)	Oregon	0.5	i.p.	0.02	15/31	48	***	
Wistar – Pott et al. (1987)	Oregon	2	i.p.	0.08	28/31	90	***	
Fischer – Wagner (1990)	Oregon	20	i.pl.	NR	30/32	94	***	
Fischer – Wagner (1990)	Oregon "short"	20	i.pl.	NR	0/32	0	NS	
Wistar – Davis et al. (1991b)	Oregon	0.005	i.p.	0.00025	0/48	0	NS	
		0.01		0.0005	4/48	8	*	
		0.05		0.0025	15/32	47	***	
		0.5		0.025	26/32	81	***	
		2.5		0.125	30/32	94	***	
		5		0.25	21/24	88	***	
		10		0.5	20/24	83	***	
		25		1.25	17/18	94	***	
Porton – Hill et al. (1990)	Oregon	0.1	i.pl.	NR	5/10	50	*	
		1		NR	9/10	90	***	
		10		NR	9/10	90	***	

Table 3.4 (continued)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres [a] [10^9]	Tumour incidence [b] n/z	%	Significance [c]	Comments
		20		NR	8/10	80	***	
Wistar – Kleymenova et al. (1999)	Grusia mines	20	i.pl.	NR	39/40	98	?	
Fischer – Coffin et al. (1992)	Oregon "C"	0.5	i.pl.	NR	123/144[d]	79	***[d]	
		2		NR		87		
		4		NR		83		
		8		NR		84		
		16		NR		87		
		32		NR		91		
Fischer – Coffin et al. (1992)	Oregon "W"	0.5	i.pl.	NR	137/144[d]	100	***[d]	
		2		NR		92		
		4		NR		100		
		8		NR		91		
		16		NR		96		
		32		NR		92		
Sprague-Dawley – Maltoni & Minardi (1989)	"Sedimentary erionite"	25	i.pl.	NR	35/40	88	***	
Sprague-Dawley – Maltoni & Minardi (1989)	"Sedimentary erionite"	25	i.p.	NR	35/40	50	***	

[a] The fibre numbers mainly refer to fibres with a length greater than 5 μm
[b] n/z number of animals with serosal tumour (mesothelioma/sarcoma) / number of animals examined
[c] calculation of the statistical significance with the Fisher exact test, one-sided: *** $p < 0.001$; ** $p < 0.01$; * $p \leq 0.05$
[d] combined data of 6 groups
i.p., intrapleural; i.pl., intraperitoneal; NS, not significant; NR, not reported
From Pott & Roller (1993b)

Table 3.5 Carcinogenicity study of intrapleural application of asbestos fibres and other fibrous materials in female Osborne-Mendel rats (40 mg fibres per rat)

Fibrous dust (material)	No. of fibres [a] (x10⁶) L > 8 µm D < 0.25 µm	Probability of pleural sarcomas [b]		Pleural sarcoma incidence [c]	
				n/z	%
Tremolite 1	55	100		22/28	79
Tremolite 2	28	100		21/28	75
Crocidolite 1	6500	94	± 6.0	18/27	67
Crocidolite 2	800	93	± 6.5	17/24	71
Crocidolite 3	4100	93	± 6.9	15/23	65
Amosite	140	93	± 7.1	14/25	56
Crocidolite 4	5400	86	± 9.0	15/24	63
Crocidolite 5 (UICC)	78	78	± 10.8	14/29	48
Crocidolite 6	1600	63	± 13.9	9/27	33
Crocidolite 7	18	56	± 11.7	11/26	42
Crocidolite 8	< 0.3[d]	53	± 12.9	8/25	32
Crocidolite 9	710	33	± 9.8	8/27	30
Crocidolite 10	49	37	± 13.5	6/29	21
Crocidolite 11	< 0.3[d]	19	± 8.5	4/29	14
Crocidolite 12	220	10	± 7.0	2/27	7
Talc 1	< 0.3[d]	7	± 6.9	1/26	4
Talc 3	< 0.3[d]	4	± 4.3	1/29	3
Talc 2	< 0.3[d]	4	± 3.8	1/30	3
Talc 4	< 0.3[d]	5	± 4.9	1/29	3
Crocidolite 13	< 0.3[d]	0		0/29	0
Talc 5	< 0.3[d]	0		0/30	0
Talc 6	80	0		0/30	0
Talc 7	< 0.3[d]	0		0/29	0

[a] Fibre numbers stated in original work as common logarithm.
[b] Calculation taking into account the different life spans (life table method).
[c] n/z = number of rats with pleural sarcomas/number of rats examined. Frequency of pleural sarcomas in female control rats: untreated, 3 animals out of 491 (0.6%); with non-carcinogenic lung implantates, 9 out of 441 (2.0%); with non-carcinogenic pleural implantates, 17 out of 615 (2.8%). [17 out of 615 against 3 out of 491, according to Fisher exact test $P < 0.01$]. All three control groups are brought together by Stanton et al. (1981) to 29 out of 1518 animals (1.9%); for this after application of the life table method a tumour probability of 7.7 ± 4.2% is indicated. [Without any reason being given it is concluded that the tumour probability in any one of the groups treated according to the life table method must exceed 30% to be "significantly" increased.] Significance limit for Fisher test in the case of 25 to 30 animals against 17 out of 615 control rats: approx. 12 to 13% tumour frequency. (The term "tumour frequency" is not to be equated with tumour probability according to the life table method. The "significance limit" of 30% mentioned by Stanton et al. (1981) refers to life table incidence or probability.
[d] The de-logarithmised fibre numbers with the above mentioned definition are between 0 and 0.3.
From Stanton et al. (1981)

8.0; 95%CI: 1.4–45.9). Lung tissue from three dogs with mesothelioma and one dog with squamous cell carcinoma of the lung had higher level of chrysotile asbestos fibres than lung tissue from control dogs (Glickman *et al.*, 1983).

3.8 Synthesis

Bronchial carcinomas and pleural mesotheliomas were observed in many experiments in rats after exposure to chrysotile, crocidolite, amosite, anthophyllite, and tremolite fibres. In these studies, there was no consistent increase in tumour incidence at other sites. A special preparation of "long" crocidolite was more effective to induce lung tumours compared to the "short" UICC asbestos samples on the basis of administered dose in f/mL.

In one study in Syrian golden hamsters with three different concentrations of amosite, a significant increase in pleural mesothelioma incidence was observed, but no lung tumours were found.

After amosite exposure and crocidolite exposure by inhalation, 2/11 baboons and 3/21 baboons developed pleural mesothelioma, respectively.

In two studies in rats exposed to erionite, a significant increase in pleural mesothelioma incidence was observed. However, no lung tumours were found.

Samples of all six asbestos types and of erionite were administered to rats by intrapleural or intraperitoneal injection in numerous studies. Consistently, mesothelioma induction was observed when samples contained a sufficient fibre number with a fibre length > 5 µm.

Only a few studies have been carried out with intratracheal instillation of crocidolite in rats and hamsters. Malignant lung tumours were observed in rats, and pleural mesothelioma and malignant lung tumours were observed in hamsters.

Chrysolite, crocidolite and amosite were administered in the feed of rats and hamsters. No increase of the incidence of gastrointestinal tumours was observed in both species.

No chronic studies with vermiculite containing asbestos fibres or talc containing asbestos fibres could be identified.

4. Other Relevant Data

4.1 Toxicokinetics, deposition, clearance, and translocation in humans

4.1.1 Aerodynamic and anatomical factors

Inhalation is the most important route of exposure to mineral fibres, and is associated with the development of non-malignant diseases of the lungs and pleura, and malignant diseases arising in the lung, larynx, and pleural and peritoneal linings (IOM, 2006). The deposition of particles and fibres in the lungs is dependent on their aerodynamic diameter, which is a function of geometry, aspect ratio (IARC, 2002), and density (Bernstein *et al.*, 2005). Fibres can deposit by sedimentation, by impaction at bronchial bifurcations or by interception of the fibre tip with the bronchial wall. Smaller diameter fibres are likely to deposit in the alveoli (Bernstein *et al.*, 2005).

Particles and fibres can be cleared from the nasal and tracheobronchial regions by mucociliary transport (Lippmann *et al.*, 1980). Following deposition in the distal airways and alveoli, short fibres are removed more slowly following phagocytosis by alveolar macrophages. Fibre length is a limiting factor in macrophage-mediated clearance; fibres longer than the diameter of human alveolar macrophages (approximately 14–25 µm) are less likely to be cleared. Fibres may also interact with lung epithelial cells, penetrate into the interstitium, and translocate to the pleura and peritoneum or more distant sites. Fibres that are not efficiently cleared or altered by physicochemical process (e.g. breakage, splitting, or

chemical modification) are termed biopersistent (Bernstein *et al.*, 2005). Chronic inhalation assays using man-made fibres in rodents have correlated fibre length and biopersistence with persistent inflammation, fibrosis, lung cancer, and malignant mesothelioma (Bernstein *et al.*, 2005). However, there are interspecies differences in alveolar deposition of inhaled particles and fibres that must be considered when extrapolating results of rodent inhalation studies to humans (IARC, 2002).

4.1.2 Biopersistence of asbestos and erionite fibres

Asbestos fibres and ferruginous bodies (described subsequently in Section 4.3.1) can be identified and quantified by tissue digestion of lung samples obtained by biopsy or at autopsy (Roggli, 1990). A variety of commercial and noncommercial asbestos fibres have been identified in residents older than 40 years of age living in an urban area with no history of occupational asbestos exposure (Churg & Warnock, 1980). These and other studies confirm that asbestos fibres are biopersistent and accumulate in lung tissue as well as lymph nodes (Dodson *et al.*, 1990; Dodson & Atkinson, 2006). Asbestos fibres have also been identified in the pleura following autopsy (Dodson *et al.*, 1990; Gibbs *et al.*, 1991; Suzuki & Yuen, 2001) and in the parietal pleural in samples collected during thoracoscopy (Boutin *et al.*, 1996). Roggli *et al.* (1980) also identified asbestos bodies in the larynx of asbestos workers at autopsy. Systemic translocation of asbestos fibres to distant organs has also been described in case reports; however, these reports should be evaluated with caution due to the numerous caveats in technical procedures used, comparison with an appropriate control population, and cross-contamination of tissue samples (Roggli, 2006). The route of translocation of asbestos fibres from the lungs to distant sites is unknown, although lymphatic translocation of amosite fibres deposited in the lungs has been shown in experimental animals (Hesterberg *et al.*, 1999; Mc Connell *et al.*, 1999; IOM, 2006; NIOSH, 2009).

Environmental exposure to erionite fibres is associated with diffuse malignant mesothelioma in three rural villages in the Cappadocia region of Turkey (Baris & Grandjean, 2006). Lung fibre digests obtained from humans in these villages showed elevated levels of erionite fibres, and ferruginous bodies surrounding erionite fibres were found in broncho-alveolar lavage fluid (Sébastien *et al.*, 1984; Dumortier *et al.*, 2001).

Talc particles have been found in the lungs at autopsy of both rural and urban residents as well as talc miners (IARC, 1987b, 2010). Talc particles are biopersistent in the lungs, and have been recovered in broncho-alveolar lavage fluid obtained from workers 21 years after cessation of occupational exposure (Dumortier *et al.*, 1989). Talc contaminated with asbestos has been linked to the development of lung cancer and malignant mesothelioma (IARC, 1987b).

The association between exposure to talc, potential retrograde translocation to the ovarian epithelium, and the development of ovarian cancer is controversial (IARC, 2010, and this volume).

The biological plausibility for an association between asbestos and ovarian cancer derives in part from the finding of asbestos fibres in the ovaries of women with potential for exposure to asbestos. Thus, a histopathological study of ovaries from 13 women who had household contact with men who had documented exposure to asbestos, and of 17 women who gave no history of potential for asbestos exposure found "significant asbestos fibre burdens" in the ovaries of nine (60.2%) of the exposed women and in only six (35%) of the unexposed women. Three of the exposed women had asbestos fibre counts in ovarian tissue of over 1 million fibres per gram (wet weight), but only one of the 17

women without exposure had counts in that range (Heller *et al.*, 1996).

Further support for the biological plausibility of an association between asbestos exposure and ovarian cancer derives from an experimental study (Graham & Graham, 1967) that found that the intraperitoneal injection of tremolite asbestos into guinea-pigs and rabbits produced epithelial changes in the ovaries "similar to those seen in patients with early ovarian cancer".

[The Working Group noted that the histopathological diagnosis of ovarian carcinoma is difficult and requires the application of immunohistochemical techniques to distinguish between this cancer and peritoneal malignant mesothelioma. These techniques and the recognition of borderline ovarian tumours and variants of serosal tumours that arise in the pelvis of women were not applied in the Graham & Graham study in 1967. In addition, mesothelial hyperplasia occurs commonly in the pelvic region, and is not considered a preneoplastic lesion (NIOSH, 2009).]

4.2 Molecular pathogenesis of human cancers related to mineral dust exposure

Cancers develop in the upper and lower respiratory tract (carcinoma of the larynx and lungs), and in the pleural and peritoneal linings (diffuse malignant mesothelioma) after a long latent period up to 20–40 years following initial exposure to asbestos or erionite fibres (IARC, 1977; IOM, 2006). During the long latent period before the clinical diagnosis of cancer of the lung or of the larynx or diffuse malignant mesothelioma, multiple genetic and molecular alterations involving the activation of cell growth regulatory pathways, the mutation or amplification of oncogenes, and the inactivation of tumour–suppressor genes characterize specific histopathological types of these tumours that have been associated with exposure to mineral dust or fibres. Some of these molecular alterations have been linked to specific chemical carcinogens in tobacco smoke (Nelson & Kelsey, 2002), and additional alterations may arise secondarily due to chronic inflammation, genetic instability, or epigenetic changes that will be discussed in detail in Section 4.3.

Additional pathways related to resistance to apoptosis, acquired genetic instability, and angiogenesis are activated or upregulated during the later stages of tumour progression of lung cancer and diffuse malignant mesothelioma (Table 4.1; Table 4.2). No mutations in oncogenes or tumour-suppressor genes have been directly linked with exposure to asbestos fibres (NIOSH, 2009).

4.2.1 Cancer of the lung and of the larynx

Lung cancers are classified into two histological subtypes: small cell carcinoma and non-small cell carcinoma (Table 4.1). In non-small cell lung carcinoma, activating point mutations in the *K-RAS* oncogene have been linked to specific chemical carcinogens in tobacco smoke; Nelson *et al.* (1999) described more frequent *K-RAS* mutations in lung carcinomas in asbestos-exposed workers. Loss of heterozygosity and point mutations in the *p53* tumour-suppressor gene have also been linked with tobacco smoke carcinogens in cancer of the lung and of the larynx (Pfeifer *et al.*, 2002; NIOSH, 2009). These alterations have also been described in lung cancers in asbestos-exposed workers (Nymark *et al.*, 2008).

4.2.2 Diffuse malignant mesothelioma

Malignant tumours arising in the pleural or peritoneal linings (diffuse malignant mesothelioma) have no association with tobacco smoking, and are characterized by a different spectrum of molecular alterations (Table 4.2). In contrast with lung cancers associated with tobacco smoking and asbestos exposure, mutations in the *K-RAS*

Table 4.1 Some reported molecular alterations in bronchogenic carcinoma

Functional alterations	Gene target	Histological type of lung cancer	
		Small cell	Non-small cell
Autocrine growth stimulation	Growth factors and receptors	GRP/GRP receptor SCF/KIT	TGF-α/EGFR HGF/MET
Activation of oncogenes	*RAS* mutation	<1%	15–20%
	MYC overexpression	15–30%	5–10%
Inactivation of tumour-suppressor genes	*p53* mutation	~90%	~50%
	RB mutation	~90%	15–30%
	$p16^{INK4A}$ inactivation	0–10%	30–70%
	FHIT inactivation	~75%	50–75%
Resistance to apoptosis	*BCL2* expression	75–95%	10–35%
Genetic instability	Microsatellite instability	~35%	~22%

EGFR, epidermal growth factor receptor; FHIT, fragile histidine triad; GRP, gastrin-releasing peptide; HGF, hepatocyte growth factor; RB, retinoblastoma gene; SCF, stem cell factor; TGF-α, transforming growth factor-α.
From Sekido et al. (2001), Sato et al. (2007), Schwartz et al. (2007), NIOSH (2009)

oncogene or the *p53* tumour-suppressor gene are rare. The most frequent molecular alteration involves deletion or hypermethylation at the *CDKN2A/ARF* locus on chromosome 9p21 which contains three tumour-suppressor genes: *p15*, $p16^{INK4A}$, and $p14^{ARF}$ (Murthy & Testa, 1999). Additional molecular alterations include hypermethylation and silencing of the *RASSFIA* and *GPC3* tumour-suppressor genes, and inactivation of the *NF2* tumour-suppressor gene (Apostolou *et al.*, 2006; Murthy *et al.*, 2000).

Comparative genomic hydrizidation, gene expression profiling, and proteomics have been used to identify specific diagnostic and prognostic biomarkers for diffuse malignant mesothelioma (Wali *et al.*, 2005; Greillier *et al.*, 2008). The most promising outcome of these global screening strategies is the identification of two potential serum or pleural fluid biomarkers that may provide early diagnosis of malignant pleural mesothelioma: osteopontin (Pass *et al.*, 2005), and soluble mesothelin-related protein (Robinson *et al.*, 2005). Both of these markers have been shown to be elevated in most patients diagnosed with diffused malignant mesothelioma, but are not entirely specific for these cancers (Greillier *et al.*, 2008). No gene expression signature can be attributed directly to asbestos exposure, and these studies show variable gene expression patterns resulting from limited stability of RNA, contamination of tumour samples with host cells, and use of different microarray platforms (López-Ríos *et al.*, 2006).

In addition to the genetic and chromosomal alterations that have been identified in diffuse malignant mesothelioma (Table 4.2), epigenetic alterations characterized by altered patterns of DNA methylation have been described (Toyooka *et al.*, 2001; Tsou *et al.*, 2005). Overall, human tumours have been characterized by global hypomethylation associated with hypermethylation of CpG islands in the promoter regions of tumour-suppressor genes leading to their inactivation. These alterations in DNA methylation are the most common molecular or genetic lesion in human cancer (Esteller, 2005). Recent comprehensive analyses of epigenetic profiles of 158 patients with malignant pleural mesotheliomas and 18 normal pleural samples using 803 cancer-related genes revealed classes of methylation profiles in malignant mesothelioma that were associated with asbestos lung burden and survival (Christensen *et al.*, 2009). Other data confirmed hypermethylation of cell-cycle

Table 4.2 Some reported molecular alterations in diffuse malignant mesothelioma

Function	Gene target	Alteration
Autocrine growth stimulation	Growth factors and receptors	HGF/MET upregulation EGFR upregulation PDGF upregulation IGF-1 upregulation
Tumour-suppressor genes	*p15, p16^INK4A^, p14^ARF^*	Inactivation or deletion
	Neurofibromin 2	*NF2* deletions, mutations
	RASSF1A, GPC3	Hypermethylation
Angiogenesis	VEGF	Upregulation
Apoptosis	*AKT*	Constitutive activation
	BCL-X	Upregulation

EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor-1; PDGF, platelet-derived growth factor; RASSF1A, Ras-association domain family 1; VEGF, vascular endothelial growth factor

From Murthy & Testa (1999), Altomare et al. (2005), Catalano et al. (2005), Kratzke & Gazdar (2005), Cacciotti et al. (2006), NIOSH (2009)

regulatory genes as well as inflammation-associated genes and apoptosis-related genes (Tsou *et al.*, 2007; Christensen *et al.*, 2008). Christensen *et al.* (2009) hypothesized that hypermethylation of specific genes confers a selective survival advantage to preneoplastic mesothelial cells in a microenvironment of persistent tissue injury and/or oxidative stress associated with exposure to asbestos fibres.

In summary, these new genomic and proteomics approaches offer promise for the discovery of novel biomarkers associated with the development of diffuse malignant mesothelioma following exposure to asbestos or erionite. No specific marker is yet available to identify those cancers.

4.3 Mechanisms of carcinogenesis

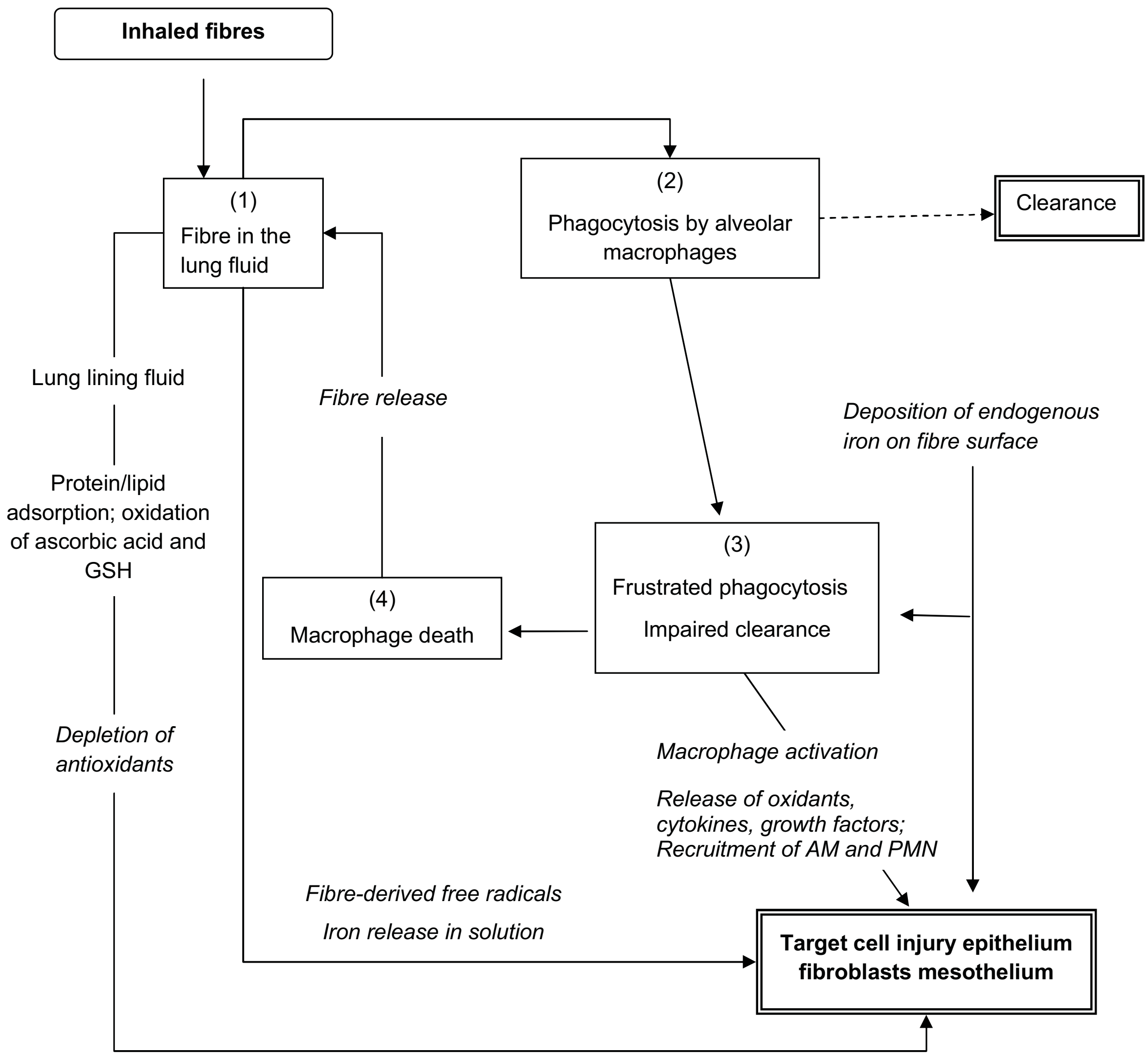
4.3.1 Physicochemical properties of mineral fibres associated with toxicity

Asbestos are natural fibrous silicates, with similar chemical composition (silica framework includes various metal cations, typically Mg^{2+}, Ca^{2+}, $Fe^{2+/3+}$, Na^{+}) mostly differing in the crystallographic constraints that yield the fibrous habit. They are poorly soluble minerals which only undergo selective leaching and incongruent dissolution. Erionite is a zeolite, which often crystallizes in thin long fibres. Major determinants of toxicity are form and size of the fibres, surface chemistry, and biopersistence. Crystal structure, chemical composition, origin, and associated minerals, as well as trace contaminants, modulate surface chemistry; and transformation, translocation, and solubility of the fibres in body fluids influence their biopersistence, a factor which modulates cumulative exposure (Fubini, 1997; Bernstein *et al.*, 2005; Fubini & Fenoglio, 2007; Sanchez *et al.*, 2009; Fig. 4.1).

(a) Crystal structure

Asbestos minerals can be divided into two groups: serpentine asbestos (chrysotile $[Mg_3Si_2O_5(OH)_4]$), and amphibole asbestos (crocidolite $[Na_2(Mg,Fe^{2+})_3Fe_2^{3+}Si_8O_{22}(OH)_2]$, amosite $[(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2]$, tremolite $[Ca_2Mg_5Si_8O_{22}(OH)_2]$, actinolite $[Ca_2(Mg,Fe^{2+})_5Si_8O_{22}(OH)_2]$, and anthophyllite $[Mg_7Si_8O_{22}(OH)_2]$). Formulae reported are ideal and are always significantly modified in nature by the occurrence of several substituting cations (e.g. $Fe^{2+/3+}$, Al^{3+}, Na^{+}). The crystal structure of chrysotile results from the association of a tetrahedral silicate sheet of composition $(Si_2O_5)_n^{2n-}$ with an octahedral brucite-like sheet of composition $[Mg_3O_2(OH)_4]_n^{2n+}$, in which iron substitutes for magnesium. The two sheets are bonded to form a 1:1 layer silicate; a slight misfit between the sheets causes curling to form

Fig. 4.1 Physicochemical properties involved in the biological activity of asbestos fibres



AMs, alveolar macrophages; PMNs, polymorphonuclear neutrophils; GSH, glutathione.
Adapted from Fubini & Otero Areán (1999), Fubini & Fenoglio (2007)

concentric cylinders, with the brucite-like layer on the outside. Van der Waals interparticle forces hold together fibrils into the actual fibre so that, when chrysotile breaks up, a large number of smaller fibres or fibrils are generated (Fubini & Otero Areán, 1999).

Amphiboles have an intrinsically elongated crystal structure which breaks up along planes within the crystal structure itself into progressively smaller fragments that generally retain a fibrous aspect. This structure can be described in terms of a basic structural unit formed by a double tetrahedral chain (corner-linked SiO_4 tetrahedra) of composition $(Si_4O_{11})_n^{6n-}$. These silicate double-chains share oxygen atoms with alternate layers of edge-sharing MO_6 octahedra, where M stands for a variety of cations: mostly Na^+, Mg^{2+}, Ca^{2+}, Fe^{2+}, or Fe^{3+} (Fubini & Otero Areán, 1999).

(b) Form and size

The pathogenic potential of asbestos depends upon its aspect ratio and fibre size. Fibre size affects respirability (respiratory zone falls off above aerodynamic diameters of 5 μm) and clearance by alveolar macrophages (section 4.1.1) (Donaldson & Tran, 2004). Short fibres are cleared more efficiently than longer ones, which undergo frustrated phagocytosis by macrophages. Short amosite fibres obtained by grinding long ones are less inflammogenic (Donaldson *et al.*, 1992), induce fewer chromosomal aberrations (Donaldson & Golyasnya, 1995), and reduce the inhibition of the pentose phosphate pathway (Riganti *et al.*, 2003). In-vitro genotoxicity studies demonstrated that both short and intermediate chrysotile asbestos fibres induced micronuclei formation and sister chromatid exchange in Chinese hamster lung cells. Intermediate fibres were more active than short fibres even when followed by treatment with dipalmitoyl lecithin, a principal constituent of pulmonary surfactant (Lu *et al.*, 1994). Long fibres but not short fibres of amosite asbestos, opsonized with rat immunoglobin, were shown to induce a dramatic enhancement of superoxide anions in macrophages isolated from rat lung (Hill *et al.*, 1995). Asbestos bodies are formed mostly on fibres longer than 20 μm (Roggli, 2004).

The role of the aspect ratio and size appears to be different for the three major asbestos-related diseases: i) asbestosis was reported as most closely associated with the surface area of retained fibres (NIOSH, 2009) although fibrosis also correlates with fibres > 2 μm long (Dodson *et al.*, 2003); ii) mesothelioma is better related to the numbers of fibres longer than about 5 μm and thinner than about 0.1 μm; and iii) lung cancer with fibres longer than about 10 μm and thicker than about 0.15 μm (NIOSH, 2009). Several studies, however, report the presence of very short fibres in lung and pleural tissue from patients with malignant mesothelioma (Dodson *et al.*, 2003; Dodson *et al.*, 2005; Suzuki *et al.*, 2005; Dodson *et al.*, 2007), suggesting caution to exclude short fibres (< 5 μm) in the development of asbestos-related diseases (Dodson *et al.*, 2003).

(c) Surface reactivity

In the last few decades, it has been accepted that, in addition to fibrous habit, surface reactivity also plays a role in the pathogenic effects of amphibole and chrysotile asbestos. The potential to release free radicals, among various other features, is considered the major determinant of the pathogenic response.

(i) Free-radical generation

Three different mechanisms of free-radical generation may take place at the surface of asbestos fibres, each one triggered by a different kind of active surface site: i) Fenton chemistry (yielding with H_2O_2 the generation of highly reactive hydroxyl radicals HO•); ii) Haber–Weiss cycle (in the absence of H_2O_2 and Fe(II), endogenous reductants allow progressive reduction of atmospheric oxygen to HO•); iii) homolytic

rupture of a carbon-hydrogen bond in biomolecules, with generation of carbon-centred radicals in the target molecule (peptides, proteins, etc.) (Hardy & Aust, 1995; Fubini & Otero Areán, 1999; Kamp & Weitzman, 1999).

Mechanism i) is relevant only in cellular compartments where H_2O_2 is present (i.e. phagolysosomal environment in macrophages), while Mechanisms ii) and iii)_may occur ubiquitously once fibres are inhaled. All mechanisms require the presence of iron ions. One stoichiometric chrysotile prepared by chemical synthesis, thus fully iron-free, was not active in free-radical generation (cell-free tests), did not induce lipid peroxidation, nor inhibit the pentose phosphate pathway in human lung epithelial cells, which is the opposite to what is found in natural specimens (Gazzano *et al.*, 2005). When loaded with less than 1 wt.% of Fe^{3+} the synthetic chrysotile also became active (Gazzano *et al.*, 2007). Asbestos fibres deprived of iron (following treatments with chelators) do not generate hydroxyl radicals (Fubini *et al.*, 1995) or damage DNA, and are less potent in causing lipid peroxidation *in vitro* (Hardy & Aust, 1995). However, not all iron ions are equally reactive in free-radical generation, depending upon their coordination and oxidation state (Shukla *et al.*, 2003; Bernstein *et al.*, 2005). Fe (II) is active even in trace amounts (Fubini *et al.*, 1995). Furthermore, Mechanism 3 requires isolated and poorly coordinated iron ions (Martra *et al.*, 2003; Turci *et al.*, 2007). The surface sites involved in this reaction are oxidized and become inactive following thermal treatments: amphibole asbestos fibres heated up to 400°C in air (Tomatis *et al.*, 2002) lose their potential in generating carboxyl radicals, but retain the reactivity for hydroxyl radicals, most likely through Mechanism 2, as long as their crystal structure is preserved. Conversely, the reduction of ferric into ferrous ions increases the radical activity (Gulumian *et al.*, 1993a). The radical yield appears unrelated to the total amount of iron (Gulumian *et al.*, 1993b), because chrysotile shows a similar behaviour to crocidolite in cell-free tests despite the lower content of iron (3–6% versus 27%). Iron oxides (magnetite, haematite) are unable to produce radical species, whereas model solids, e.g zeolites enriched with small amount of iron but with ions poorly coordinated and mostly in low valence state, are very reactive, particularly in hydrogen abstraction (Fubini *et al.*, 1995).

Iron-derived free radicals are believed to produce a variety of cell effects including lipid peroxidation (Ghio *et al.*, 1998; Gulumian, 1999), DNA oxidation (Aust & Eveleigh, 1999), TNF-release and cell apoptosis (Upadhyay & Kamp, 2003), adhesion (Churg *et al.*, 1998), and an increase of fibre uptake by epithelial cells (Hobson *et al.*, 1990).

(ii) Iron bioavailability and biodeposition

Iron can be removed from asbestos fibres by intracellular chelators. If iron is mobilized from low–molecular-weight chelators, e.g. citrate, redox activity may be altered. The chelator–iron complex can diffuse throughout the cell, and catalyse the formation of hydroxyl radicals. Mobilization of iron was shown to correlate with DNA strand breaks and with DNA oxidation induced by crocidolite, amosite, and chrysotile (Hardy & Aust, 1995). In human lung epithelial and pleural mesothelial cells, the extent of iron mobilization was also related to the inactivation of epidermal growth factor receptor (EGFR/ErbB1), a step in the pathway leading to apoptosis (Baldys & Aust, 2005).

Mineral fibres may also acquire iron which, under certain conditions, may modify their reactivity. Erionite (Dogan *et al.*, 2008) is able to bind both ferrous (through ion exchange) and ferric ions (through a precipitation or crystallization process). After ferrous-binding, erionite acquires the ability to generate hydroxyl radicals, and to catalyse DNA damage (DNA single-strand breaks); and after ferric-binding, the reactivity is acquired only in the presence of a reductant

(Hardy & Aust, 1995; Fach *et al.*, 2003; Ruda & Dutta, 2005). During their residence in the lung, asbestos fibres, like erionite fibres, acquire iron via a complex mechanism that may originate from the adsorption and disruption of ferritin, eventually yielding ferruginous bodies. These so-called asbestos bodies are preferentially formed onto long amphibole fibres but have also been found onto chrysotile fibres (Roggli, 2004). Although the presence of asbestos bodies in asbestos-related diseases is well documented, their biological role is still controversial. Iron deposition was thought to protect cells (Ghio *et al.*, 1997), but, deposited iron may become redox-active, thus enhancing the catalytic potential of the fibres (Ghio *et al.*, 2004). Asbestos bodies with amosite cores caused DNA single-strand breaks (Lund *et al.*, 1994); and increased radical damage to DNA was reported for ferritin-covered amosite in the presence of ascorbic acid (Otero-Areán *et al.*, 1999). Asbestos fibres might also disrupt normal iron homeostasis in the host by mobilizing and accumulating this metal (Ghio *et al.*, 2008).

Binding Fe (II) from solution increases iron mobilization from crocidolite by chelators, and induces DNA single-strand breaks. Increased lipid peroxidation and release of leukotriene B4 is found in alveolar macrophages from rats treated with Fe (III)-loaded crocidolite, and Fe (III)-loaded crocidolite fibres induce more DNA single-strand breaks *in vitro* than do untreated crocidolite fibres (Ghio *et al.*, 1992).

It was suggested that crocidolite stimulates inductible nitric oxide synthase by decreasing iron bioavailability (Aldieri *et al.*, 2001).

(d) Biopersistence, biodurability, and ecopersistence

The residence time in the lung depends upon both the clearance mechanisms and physico-chemical processes taking place. Clearance mechanisms are mainly related to the shape and size of the particle, whereas chemical composition, surface area, and structural parameters mainly affect leaching, dissolution, and breakage.

Selective leaching is more pronounced for serpentine asbestos than for amphiboles, which have no leachable "weak points" in their structure. Selective leaching of chrysotile occurs under strong acidic or chelating conditions, resulting in removal of Mg^{2+} ions. The kinetics vary according to the origin of the material, mechanical treatments, and associated contaminants, e.g. presence of nemalite (fibrous brucite) (Morgan, 1997). Chrysotile may lose magnesium *in vivo*, following phagocytosis by alveolar macrophages. The biological potential of magnesium-depleted chrysotile is greatly decreased (Langer & Nolan, 1994; Gulumian, 2005). Furthermore, leached fibres undergo breakage into shorter fibres, which may be cleared more readily from the lung. This accounts for the relatively low biopersistence of chrysotile compared to the amphiboles. The lungs of some chrysotile workers at autopsy contain low levels of chrysotile but substantial numbers of tremolite fibres, which is present in some chrysotile-bearing ores. For this reason, tremolite has been suggested to contribute to the carcinogenic effects seen in chrysotile miners (McDonald *et al.*, 1997; McDonald & McDonald, 1997; McDonald, 1998). Other asbestiform minerals may be associated with chrysotile, and, in some cases, modulate its toxicity, depending upon their amount and physicochemical characteristics. Balangeroite, occasionally intergrows with chrysotile (up to 5%) in the Balangero mine (Italy) and its sourroundings. Balangeroite fibres have a different structure from amphiboles, and are poorly eco- and bio-durable (Favero-Longo *et al.*, 2009; Turci *et al.*, 2009). Balangeroite may contribute to the overall toxicity of chrysotile, but it cannot be compared to tremolite nor considered to be solely responsible for the excess of mesothelioma found in Balangero (Mirabelli *et al.*, 2008).

In the natural environment, weathering processes carried out by micro-organisms

may induce chrysotile-leaching, contributing to its bioattenuation (Favero-Longo *et al.*, 2005). However, the dissolution of chrysotile is very low, because any breakdown of the silica framework takes place at a slow rate (Hume & Rimstidt, 1992), and is limited to a few layers in mild conditions (Gronow, 1987). Even in a strong acidic environment, the final product still retains a fibrous aspect at the nanoscale which is devoid of cations (Wypych *et al.*, 2005).

4.3.2 Direct genotoxicity

Mineral fibres may directly induce genotoxicity by catalysing the generation of reactive oxygen species resulting in oxidized DNA bases and DNA strand breaks that can produce gene mutations if not adequately repaired (IOM, 2006). Both asbestos and erionite fibres can induce DNA damage mediated by reactive oxygen species. Asbestos fibres have also been shown to physically interfere with the mitotic apparatus, which may result in aneuploidy or polyploidy, and specific chromosomal alterations characteristic of asbestos-related cancer (Jaurand, 1996).

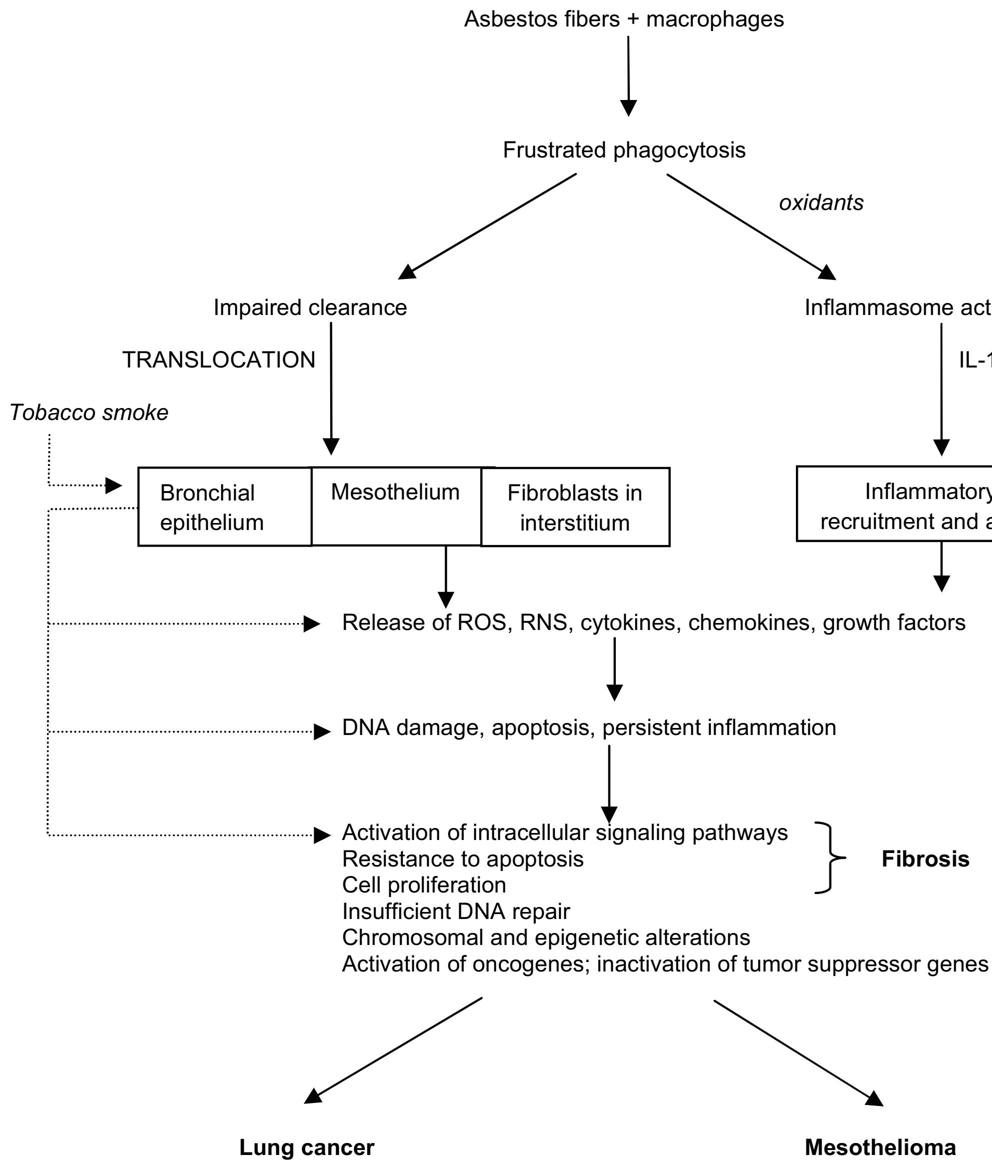
In addition to direct clastogenic and aneuploidogenic activities that may be induced following the translocation of asbestos fibres to target cell populations in the lungs, persistent inflammation and macrophage activation can secondarily generate additional reactive oxygen species, and reactive nitrogen species that can indirectly induce genotoxicity in addition to activation of intracellular signalling pathways, stimulation of cell proliferation and survival, and induction of epigenetic alterations (Fig. 4.2).

4.3.3 Indirect mechanisms

Asbestos fibres have unique and potent effects on alveolar macrophages that have been postulated to trigger the chain of events leading to chronic lung fibrosis (asbestosis), and lung cancer (Shukla *et al.*, 2003). Macrophages express a variety of cell-surface receptors that bind to mineral fibres leading to phagocytosis, macrophage apoptosis, or macrophage activation. Receptors expressed by macrophages and other target cells in the lung that bind mineral fibres include MARCO, a scavenger receptor class A, and integrin receptors (Boylan *et al.*, 1995; Gordon *et al.*, 2002; Arredouani *et al.*, 2005). Macrophage apoptosis has also been postulated to contribute to an increased incidence of autoimmune diseases in residents in Libby, Montana, USA, who are exposed to vermiculite contaminated with amphibole asbestos fibres (Noonan *et al.*, 2006; Blake *et al.*, 2008).

Phagocytosis of asbestos fibres leads to the excess generation of reactive oxygen and nitrogen species by both direct (described in Sections 4.3.1 and 4.3.2), and indirect mechanisms (Manning *et al.*, 2002). Alveolar macrophages phagocytize particulate materials and micro-organisms leading to assembly of NADPH oxidase in the phagolysosomal membrane that generates reactive oxygen species, which are potent antimicrobial agents. Asbestos fibres have elevated surface reactivity and redox-active iron that can generate hydroxyl radicals leading to lipid peroxidation, protein oxidation, and DNA damage resulting in lung injury that is amplified by persistent inflammation (Fig. 4.1 and 4.2). Recent investigations in genetically engineered mice have provided evidence for a key role of the NALP3 inflammasome as an intracellular sensor of the initial interactions between asbestos fibres and other crystals such as monosodium urate with macrophages (Yu & Finlay, 2008). The NALP3 inflammasome activates caspase-1 that cleaves IL-1β precursor to active IL-1β that is rapidly secreted (Cassel *et al.*, 2008; Dostert *et al.*, 2008). This cytokine then triggers the recruitment and activation of additional inflammatory cells and the release of additional cytokines including TNF-α, IL-6, and IL-8 that perpetuate a prolonged inflammatory response to these biopersistent mineral dusts (Shukla *et al.*, 2003).

Fig. 4.2 Proposed mechanism for the carcinogenicity of asbestos fibres



IL-1β, interleukin -1β; RNS, reactive nitrogen species; ROS, reactive oxygen species.
Adapted from Shukla et al. (2003), Kane (2006), Nymark et al. (2008)

The generation of reactive oxygen species by asbestos fibres has also been associated with inducing apoptosis in mesothelial cells (Broaddus *et al.*, 1996), and alveolar epithelial cells (Aljandali *et al.*, 2001).

Asbestos fibres have been shown to contribute to the transformation of a variety of target cells from different species *in vitro*, and to induce lung tumours and malignant pleural mesothelioma in rodents following chronic inhalation (Bernstein *et al.*, 2005). There are important species differences in the induction of asbestos-related cancers: rats are more susceptible to the induction of lung cancer, and hamsters are resistant to the induction of lung cancer but more susceptible to the development of malignant pleural mesothelioma (IARC, 2002). Subchronic inhalation studies using refractory ceramic fibres (RCF-1) suggest that the increased susceptibility of hamsters to developing malignant pleural mesothelioma may be related to greater translocation and accumulation of fibres in the pleural space, and an increased mesothelial cell proliferation in hamsters compared to rats (Gelzleichter *et al.*, 1999). There are serious limitations in extrapolating these species differences to humans. First, most human lung cancers, even in asbestos-exposed individuals, are confounded by tobacco smoke that has potent independent genotoxic effects as reviewed later in Section 4.4.1. Second, diffuse malignant mesothelioma in humans is usually diagnosed at an advanced stage, and there are no reliable premalignant changes or biomarkers that may provide clues about the molecular pathogenesis of mesothelioma associated with exposure to asbestos or erionite fibres (NIOSH, 2009).

A unifying mechanism based on the experimental in-vitro cellular and in-vivo rodent models is proposed in Fig. 4.2.

Recent biochemical studies have confirmed that oxidative damage to cytosine is a plausible biological mechanism leading to epigenetic alterations and development of cancer in association with persistent inflammation (Valinluck & Sowers, 2007). Neutrophils and macrophages are the source of reactive oxygen and nitrogen species triggered by phagocytosis of crystalline silica (quartz) or asbestos fibres. In addition, myeloperoxidase catalyses the formation of hypochlorous acid (HOC1) in neutrophils, and a specific peroxidase catalyses the formation of hypobromous acid (HOBr) in eosinophils (Babior, 2000). The formation of 8-oxoguanine, 5-hydroxymethylcytosine, or 5-hydroxycytosine interferes with DNA methylation and binding of methyl-CpG binding domains (MBDs). In contrast, chlorination or bromination of cytosine mimics 5-methylcytosine and induces heritable DNA methylation at previously unmethylated sites. Halogenated cytosines are also recognized by MBDs to facilitate chromatin remodelling. However, these modified bases are not recognized by DNA glycosylase, and are not repaired (Valinluck & Sowers, 2007).

This hypothesis linking heritable alterations in patterns of cytosine methylation with endogenous sources of oxidants released from inflammatory cells is a plausible explanation for the development of lung cancer and diffuse malignant mesothelioma associated with exposure to mineral fibres. Elevated neutrophils and eosinophils have been found in the pleural space following the inhalation of refractory ceramic fibres by hamsters and rats (Gelzleichter *et al.*, 1999). Furthermore, myeloperoxidase activity has been detected in rodent lungs following exposure to asbestos fibres, whereas a decreased lung inflammation was observed in asbestos-exposed myeloperoxidase-null mice (Haegens *et al.*, 2005). This indirect mechanism secondary to persistent inflammation may be responsible for altered epigenetic methylation profiles, which are characteristic of human malignant pleural mesotheliomas (Christensen *et al.*, 2009).

4.4 Susceptible populations

Both exogenous environmental and occupational exposures and endogenous factors including genetic susceptibility contribute to the development of lung cancer (NIOSH, 2009) and diffuse malignant mesothelioma (Weiner & Neragi-Miandoab, 2009). The best example of an exogenous exposure that is a major cofactor with asbestos fibres in the development of cancer of the larynx and of the lung is tobacco smoking (Table 4.3; Table 4.4; IARC, 2004; IOM, 2006). Additional environmental and occupational exposures are also risk factors for cancer of the larynx (Table 4.3) and of the lung (Table 4.4); these exposures are potential confounders in human epidemiological studies (IOM, 2006). Specific examples of these cofactors and other environmental and occupational exposures will be described in relationship to mechanisms of these cancers associated with mineral dust exposures.

4.4.1 Other risk factors for cancer of the lung and of the larynx, and diffuse malignant mesothelioma

(a) Tobacco smoke

Co-exposure to tobacco smoke and asbestos fibres is at least additive and possibly multiplicative in the development of lung cancer (Vainio & Boffetta, 1994). The inhalation of tobacco smoke (Walser *et al.*, 2008) as well as mineral fibres is associated with excess generation of reactive oxygen and nitrogen metabolites, cell injury and apoptosis, and persistent lung inflammation (Shukla *et al.*, 2003; IARC, 2004). Excess oxidant generation has been shown to enhance the penetration of asbestos fibres into respiratory epithelial cells, and to impair fibre clearance (McFadden *et al.*, 1986; Churg *et al.*, 1989), as well as altering the metabolism and detoxification of tobacco smoke carcinogens (Nymark *et al.*, 2008). Asbestos fibres can also adsorb tobacco smoke carcinogens and metals and facilitate their transport into the lungs (IOM, 2006). Asbestos fibres have also been shown to activate growth-factor receptors and cell-signalling pathways that stimulate cell proliferation and promote cell survival (Albrecht *et al.*, 2004). In summary, co-exposures to tobacco smoke and mineral fibres can amplify acquired genetic mutations induced by tobacco smoke carcinogens, and amplify cell proliferation in response to tissue injury leading to an increased risk for the development of cancer of the larynx and of the lung (Nymark *et al.*, 2008).

Table 4.3 Risk factors for the development of cancer of the larynx

Exposure	Reference
Active tobacco smoking	IARC (1986, 2004, 2012d)
Alcohol	IARC (1988, 2010, 2012d)
Mustard gas	IARC (1987a, 2012e)
Inorganic acid mists containing sulfuric acid	IARC (1992, 2012e)
Asbestos fibres	IOM (2006), IARC (2012b)
Human papilloma virus (HPV): types 6, 11, 16, 18 limited evidence	IARC (2007, 2012c)

Compiled by the Working Group

(b) Other occupational and environmental exposures

Alcohol and occupational exposure to irritants (Table 4.3) also contribute to the development of cancer of the larynx. These irritants, similar to inhalation of tobacco smoke, can cause repeated episodes of injury to the respiratory epithelium, resulting in metaplasia and dysplasia (Olshan, 2006); these preneoplastic lesions may then acquire additional molecular alterations and progress towards the development of invasive lung or laryngeal carcinoma. Other occupational exposures responsible for the development of lung cancer include direct-acting carcinogens such as ionizing radiation (IARC, 2000, 2012a), and metals (reviewed in IARC, 2012b).

Table 4.4 Risk factors for the development of cancer of the lung

Exposure	Reference
Active and passive tobacco smoking	IARC (2004, 2012d)
Ionizing radiation	IARC (2000, 2012a)
Respirable dusts and fibres:	
Asbestos	IARC (1987a, 2012b)
Talc containing asbestiform fibres	IARC (1987a, 2012b)
Erionite	IARC (1987a, 2012b)
Crystalline silica (quartz)	IARC (1997, 2012b)
Vermiculite contaminated with asbestos fibres	Amandus & Wheeler (1987), McDonald et al. (2004), IARC (2012b)
Bis(chloromethyl)ether and chloromethyl methyl ether	IARC (1987a, 2012e)
Arsenic and arsenic compounds	IARC (1987a, 2012b)
Beryllium	IARC (1993, 2012b)
Cadmium and cadmium compounds	IARC (1993, 2012b)
Hexavalent chromium	IARC (1990, 2012b)
Nickel sulfate, oxides, and sulfides	IARC (1990, 2012b)
Soots	IARC (1985, 1987a, 2012e)

Compiled by the Working Group

The strongest risk factors associated with the development of diffuse malignant mesothelioma include environmental or occupational exposures to erionite, asbestos fibres, and talc or vermiculite contaminated with asbestos fibres (Table 4.5; NIOSH, 2009). It is unknown whether the carcinogenic effects of exposure to mixed dusts contaminated with asbestos fibres can be entirely attributed to the asbestos fibres or whether co-exposure to talc or vermiculite dusts potentiates the retention and/or biological activity of asbestos fibres *in vivo* (Davis, 1996). The occurrence of talc pneumoconiosis and its relationship to other mineral dust contaminants including quartz and tremolite was recently reviewed (IARC, 2010). In-vitro assays of talc cytotoxicity were also summarized (IARC, 2010). No experimental studies have been published assessing the cytotoxicity of vermiculite contaminated with asbestos fibres. A sample of the mixture of amphibole fibres associated with Libby vermiculite ore has been shown to induce cytotoxicity and oxidative stress in macrophages *in vitro* (Blake *et al.*, 2007).

(c) SV40 and HPV viruses

Two human DNA tumour viruses have been linked with an increased risk for cancer of the larynx (Table 4.3; high-risk subtypes of human papillomavirus (HPV)) and diffuse malignant mesothelioma (Table 4.5; Simian virus 40 (SV40)).

The evidence for HPV 16 in the development of cancer of the larynx has been evaluated as limited, although it has been implicated as an independent risk factor in the development of other squamous cell carcinomas arising in the head and neck region (IARC, 2007, 2012c).

The association between exposure to SV40 and asbestos fibres in the development of diffuse malignant mesothelioma is highly controversial (Butel & Lednicky, 1999; Gazdar *et al.*, 2002; Shah, 2004; IOM, 2006). SV40 is not an essential cofactor for the development of mesothelioma; for example, residents of the Cappadocian villages in Turkey have a very high risk for diffuse malignant mesothelioma but do not have evidence of SV40 exposure (Dogan *et al.*, 2006). Although there are several in-vitro mechanistic

Table 4.5 Risk factors for the development of diffuse malignant mesothelioma

Exposure	Reference
Asbestos fibres	IARC (1987a, 2012b)
Erionite	IARC (1987a, 2012b)
Talc containing asbestiform fibres	IARC (1987a, 2012b)
Vermiculite contaminated with asbestos fibres	Amandus & Wheeler (1987), IARC (1987a, 2012e), McDonald et al. (2004)
Thorotrast	IARC (2001, 2012a)

Compiled by the Working Group

studies that support a role for SV40 viral oncogenes in the transformation of mesothelial cells, the human epidemiological evidence is inconclusive to support a causal association (Weiner & Neragi-Miandoab, 2009).

4.4.2 Genetic susceptibility

(a) Cancer of the lung

Tobacco smoke is the major cause of cancer of the lung; however, only a few rare hereditary syndromes are associated with an increased risk of lung, as well as other cancers: Bloom syndrome, Li-Fraumeni syndrome, and hereditary retinoblastoma (Lindor *et al.*, 2006). Other genetic polymorphisms in genes related to the metabolism and detoxification of tobacco smoke carcinogens, antioxidant defenses, and DNA repair have been suggested as predisposing factors for the development of lung cancer, although individually they contribute minimally to an increased risk (IOM, 2006). Attempts have been made to identify genetic polymorphisms in enzymes involved in xenobiotic metabolism and antioxidant defense that increase the risk for asbestos-related lung cancer; however, no consistent associations have been found (Nymark *et al.*, 2008).

(b) Diffuse malignant mesothelioma

With the exception of certain populations who have been exposed environmentally to asbestos or erionite fibres since birth (NIOSH, 2009), the development of diffuse malignant mesothelioma even in occupationally exposed workers is less common than the development of lung cancer (Nymark *et al.*, 2008). This observation has led to the hypothesis that there may be a genetic predisposition to the development of diffuse malignant mesothelioma following exposure to asbestos or erionite fibres. Isolated case reports provide examples of diffuse malignant mesothelioma in patients with neurofibromatosis type 2 (Baser *et al.*, 2002) or Li-Fraumeni syndrome (Heineman *et al.*, 1996) who are also exposed to asbestos. Several reports of familial cases of diffuse malignant mesothelioma are complicated by a common household exposure history (Weiner & Neragi-Miandoab, 2009). The strongest association between environmental exposure to erionite and genetic susceptibility to diffuse malignant mesothelioma has been provided by pedigree analysis of residents in the Cappadocia region of Turkey (Dogan *et al.*, 2006). However, there is skepticism about the accuracy of this analysis, and a recent review indicated that familial clusters can account for only 1.4% of cases of mesothelioma in Italy between 1978–2005 (Ascoli *et al.*, 2007; Ugolini *et al.*, 2008). One study has reported an association between genetic polymorphisms in the X-ray complementing group 1 gene (XRCC1) and the development of malignant mesothelioma in a population exposed to asbestos fibres (Dianzani *et al.*, 2006). More sensitive genome-wide association studies may uncover new markers for genetic susceptibility that predict increase risks of developing diffuse malignant mesothelioma following exposure to asbestos or erionite fibres.

4.5 Synthesis

The mechanistic basis for asbestos carcinogenicity is a complex interaction between crystalline mineral fibres and target cells *in vivo*. The most important physicochemical properties of asbestos fibres related to pathogenicity are surface chemistry and reactivity, surface area, fibre dimensions, and biopersistence. Multiple direct and indirect mechanisms have been proposed based on numerous in-vitro cellular assays, and acute and subchronic animal bioassays. These complex mechanisms most likely interact at multiple stages during the development of lung cancer and diffuse malignant mesothelioma.

The following general mechanisms have been proposed for the carcinogenicity of asbestos fibres (Fig. 4.1; Fig. 4.2):

1. Direct interaction between asbestos fibres and target cells *in vitro*:
   - Asbestos and erionite fibres have been shown to generate free radicals that directly induce genotoxicity as assessed by DNA breaks and oxidized bases in DNA.
   - Asbestos fibres have also been shown to interfere with the mitotic apparatus by direct physical interaction resulting in aneuploidy and polyploidy.
2. Indirect mechanisms:
   - In laboratory animals, asbestos fibres have been shown to induce macrophage activation and persistent inflammation that generate reactive oxygen and nitrogen species contributing to tissue injury, genotoxicity, and epigenetic alterations. Persistent inflammation and chronic oxidative stress have been associated with the activation of intracellular signalling pathways, resistance to apoptosis, and stimulation of cell proliferation.

There are significant species differences in the responses of the respiratory tract to the inhalation of asbestos fibres. The biological mechanisms responsible for these species differences are unknown. Based on comparative animal experimental studies, there may be differences in deposition and clearance of fibres in the lungs, in severity of fibrosis, in kinetics of translocation of fibres to the pleura, and in levels or types of antioxidant defense mechanisms.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite). Asbestos causes mesothelioma and cancer of the lung, larynx, and ovary. Also positive associations have been observed between exposure to all forms of asbestos and cancer of the pharynx, stomach, and colorectum. For cancer of the colorectum, the Working Group was evenly divided as to whether the evidence was strong enough to warrant classification as *sufficient*.

There is *sufficient evidence* in experimental animals for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite).

There is *sufficient evidence* in humans for the carcinogenicity of talc containing asbestiform fibres. Talc containing asbestiform fibres causes cancer of the lung and mesothelioma.

There is *inadequate evidence* in experimental animals for the carcinogenicity of talc containing asbestiform fibres.

All forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite) are *carcinogenic to humans (Group 1).*

Talc containing asbestiform fibres is *carcinogenic to humans (Group 1)*

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ERIONITE

Erionite was considered by previous IARC Working Groups in 1987 (IARC, 1987a, b). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

Erionite (CAS Registry No.: 66733-21-9) is a naturally occurring fibrous mineral that belongs to a group of hydrated aluminosilicate minerals called zeolites (NTP, 2004). Its molecular formula is $(Na_2, K_2, Ca, Mg)_{4.5}Al_9Si_{27}O_{72}{\bullet}27H_2O)$ (IARC, 1987a).

1.2 Chemical and physical properties of the agent

Erionite is a natural fibrous zeolite, found in certain volcanic tuffs as an environmental contaminant. The basic structure of erionite series minerals is an aluminosilicate tetrahedron ($(Si,Al)O_4$) with oxygen atoms shared between two tetrahedra. Erionite is a 'chain silicate' composed of six tetrahedra on each edge of the unit (NTP, 2004). Although erionite has a similar morphology to that of amphibole asbestos (i.e. it has a chain-like structure), it has different chemical and physical properties (Metintas *et al.*, 1999). Erionite occurs as finely fibrous or wool-like white prismatic crystals, with a hexagonal physical structure, and an internal surface area approximately 20 times larger than that of crocidolite asbestos (IARC, 1987a; Metintas *et al.*, 1999; NTP, 2004). It has a density between 2.02–2.08, and absorbs up to 20% of its weight in water. Its gas absorption, ion exchange, and catalytic properties are highly selective and dependent upon the molecular or ionic size of the sorbed compounds as well as upon the cation content of erionite itself (IARC, 1987a). Erionite is not known to occur in other than fibrous form; however, the detailed morphology of erionite 'bundles' that are composed of many 'fibres' and 'fibrils' enhances its surface-area-to-volume ratio drastically (Dogan *et al.*, 2008).

1.3 Use of the agent

Natural zeolites have many commercial uses, most of which are based on the ability of these minerals to selectively adsorb molecules from air or liquids. Erionite has been used as a noble-metal-doping catalyst in a hydrocarbon-cracking process, and studied for its use in agricultural applications (i.e. in fertilizers and odour control in livestock production) (IARC, 1987a; NTP, 2004). Erionite-rich blocks were historically quarried in the western United States of America for house-building materials, but this use was considered very minor, and not an

intentional use of erionite itself (IARC, 1987a). Natural erionite has not been mined or marketed for commercial purposes since the late 1980s, and has been replaced by synthetic non-fibrous zeolites (Dogan & Dogan, 2008).

1.4 Environmental occurrence

1.4.1 Natural occurrence

Zeolite minerals are found as major constituents in numerous sedimentary volcanic tuffs, especially where these have been deposited and altered by the action of saline lake water (either by percolation or immersion). Erionite minerals occur as deposits of prismatic-to-acicular crystals in several different types of rock (e.g. rhyolite tuff), and in a wide range of geological settings. They rarely occur in pure form and are normally associated with other zeolite minerals (e.g. clinoptilolite, clinoptilolite-phillipsite). Erionite occurs as two major morphotypes: a short fibre form (named after the original Greek word for wool), and a long fibre form. When ground to powder, erionite fibres resemble amphibole asbestos fibres morphologically (IARC, 1987a; Dogan & Dogan, 2008).

Deposits of erionite have been recorded in Antarctica, Europe (Austria, the Czech Republic, France, Germany, Italy), Africa (Kenya, United Republic of Tanzania), Asia (the Republic of Korea, Japan), North America (USA, Canada, Mexico), as well as Georgia, Iceland, New Zealand, the Russian Federation, Scotland, and Turkey (Dogan & Dogan, 2008; Ilgren *et al.*, 2008).

The fibre size distribution of erionite from different deposits vary. Turkish erionite from Karain contains a higher proportion (32%) of longer fibres (> 4 µm) than erionite from Oregon, USA (11%) or New Zealand (8%). New Zealand and Oregon erionites contain 2–3% of thicker fibres (> 1 µm), whereas Karain erionite does not contain any such fibres (Ilgren *et al.*, 2008).

1.5 Human exposure

1.5.1 Exposure of the general population

Most of the non-occupational data on exposure to erionite refers to certain villages of the Cappadocia region, Turkey, where people are exposed to erionite throughout their lives. Erionite deposits in the USA are in remote desert regions where there is no stable population (Dogan *et al.*, 2008).

Dumortier *et al.* (2001) evaluated the fibre burden in bronchoalveolar lavage fluid (BALF) of 16 inhabitants of Tuzköy, an erionite-exposed village in the Cappadocia region of Turkey. All subjects were considered to have environmental exposure to erionite (because they were born in the village and had lived there for 10 years). Their fibre burden was compared to that of subjects with ($n = 59$) and without ($n = 16$) environmental exposure to tremolite asbestos. Ferruginous bodies (FBs) and fibres in the BALF were measured and analysed by phase–contrast light and transmission electron microscopy (TEM). FBs were detected by light microscopy in the BALF of 12 subjects; of these, seven had concentrations above 1 FB/mL. The geometric mean concentration of FBs was 1.33 FB/mL (95%CI: 0.35–3.04). In the TEM analysis, erionite accounted for 95.7% of the FBs. Erionite fibres were found in the BALF of all 16 subjects; nine subjects had concentrations higher than 300 f/mL. The mean concentration of erionite fibres in BALF was similar to that of tremolite fibres in subjects with environmental exposure to tremolite. Erionite accounted for 35.6% of fibres longer than 8 µm in BALF. Tremolite, in contrast, accounted for 14.0%. The asbestos fibre concentrations in erionite villagers was not different from that in subjects without environmental exposure to tremolite.

1.5.2 Occupational exposure

Historically, occupational exposure occurred from the mining and production of erionite. Erionite has also been reported to be a minor component in some commercial zeolites. Although erionite has not been mined for commercial purposes since the late 1980s, occupational exposure to erionite may still occur during the mining, production, and use of other zeolites (NTP, 2004).

2. Cancer in Humans

2.1 Pleural and peritoneal mesothelioma

At the end of the 1970s, a very high incidence of pleural mesothelioma was observed in one of the regions of Turkey, in three villages in Cappadocia where erionite was present (Sarihidir, Tuzköy, and Karain). During 1970–87, 108 cases of pleural mesothelioma were recorded in the small village of Karain (604 inhabitants in 1974) – equivalent to an annual incidence of more than 800 cases/100000, that is, about 1000 times the rate observed in the general population of industrialized countries. These cases were responsible for nearly half the deaths reported in this village. In Tuzköy, the annual incidence was estimated at 220 cases/100000. Overall, it was identical for men and women, the ratio of men/women was in the range of 1–2, according to series and village, and the mean age was roughly 50, with a range of 26–75 years (Bariş *et al.*, 1978; Simonato *et al.*, 1989). Artvinli & Bariş (1979) suggested that the presence of erionite in the soil, road dust and building stones of Tuzköy was probably the cause of the high incidence of mesothelioma, and other respiratory abnormalities. It was estimated that a cumulative yearly dose of 1 f/mL induces a pleural mesothelioma rate of 996/100000 persons–year in erionite villages (Simonato *et al.*, 1989).

Bariş & Grandjean (2006) extended the follow-up of the inhabitants of Sarihidir and Karain and another village without known exposure to erionite during 1979–2003. A total of 891 men and women, aged 20 years or older, were included, 230 of them from the village without exposure. During the 23-year follow-up, 372 deaths occurred; 119 of these from mesothelioma, which was the cause of 44.5% of all deaths in the exposed villages. Seventeen patients had peritoneal mesothelioma; the rest had pleural mesothelioma. Only two cases of mesothelioma, one of each type, occurred in the control village—both in women born elsewhere. When standardized to the world population, the pleural mesothelioma incidence was approximately 700 and 200 cases per 100000 people annually in the two exposed villages, respectively, and about 10 cases per 100000 people in the control village.

Other studies were published on a cohort of nearly 100 Karain natives who had emigrated to Sweden from the 1960s onwards. In the first of these, seven cases (four women, three men) of mesothelioma were observed (Özesmi *et al.*, 1990). In a follow-up to 1997 including 162 subjects (87 men and 75 women), Metintas *et al.* (1999) reported 14 (78%) deaths due to mesothelioma among the overall 18 deaths during 1965–97; this proportion was even higher than the proportion found in a Turkish study (49%) (Bariş *et al.*, 1996). The fact that the immigrant community was stable, and the diagnoses of mesothelioma were all histopathologically proven, gives strength to the findings. The average annual mesothelioma incidence rates in this cohort were about 135 times higher among the men and 1336 times higher among the women compared with the general population of Sweden during 1965–67. The total observed number of malignant pleural mesotheliomas (eight men and ten women) in this group resulted in a risk (mesothelioma standardized incidence ratio) in the men and women subjects of about 265 and 1992 times higher, respectively, than that of the

Swedish population (Metintas *et al*., 1999). The men/women ratio of pleural mesothelioma in the cohort (0.8) was different from that of industrialized countries, where mesothelioma mostly occurs due to occupational exposure. Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-07-Table2.1.pdf presents the main results of pleural mesothelioma incidence and mortality in populations exposed to erionite in Cappadocia, Turkey.

Selçuk *et al*. (1992) studied 135 mesothelioma cases in Turkey from erionite (*n* = 58) and tremolite (*n* = 77) villages. The clinico-anatomical appearance of the malignancies was similar in subjects exposed to asbestos or erionite fibres, and pleural plaques were observed in all subjects. In both the erionite- and the asbestos-exposed groups, one quarter of the patients were less than 40 years of age, and the mean ages were not significantly different between the two groups (respectively, 46.4 and 49.7 years); the ages of the patients were in the range of 27–67 years in the erionite group and 26–75 years in the asbestos group, suggesting that the latent period was not specific to the type of fibre that patients were exposed to. Men and women were approximately equal in number in the erionite group (men/women ratio: 31:27); and men were the predominant gender in the asbestos group (men/women ratio: 51:26). However, this may be explained in part by referral bias, as populations from the three erionite villages were known as a high-risk group, and the patients were referred as soon as a presumptive diagnosis was made; in contrast, there was no equivalent system of survey in the asbestos villages where patients were not actively surveyed, but were admitted after presentation.

Gulmez *et al*. (2004) retrospectively evaluated 67 patients with mesothelioma observed during 1990–2001 in central Anatolia, Turkey. In 51 patients (76.1%), the mesothelioma was confined to the pleura, in 14 patients it was exclusively peritoneal, and in two patients, it involved both areas. Of the 67 cases, 35 (52.2%) were women; the mean age for all cases was 57.6 years. Environmental exposure to erionite and asbestos was found in 50.7% and 25.4% of the cases, respectively.

Some of the studies of erionite-induced mesothelioma in Turkey could not rely on full diagnosis assessment. X-rays and biopsy histology were available for many cases, but not for all. However, some studies were able to perform full histopathological examinations, such as the Selçuk *et al*. (1992) study, or the Swedish study of Karain emigrants (Özesmi *et al*., 1990; Metintas *et al*., 1999), and found associations of the same order of magnitude between erionite exposure and the risk of mesothelioma, giving strong confidence in the Turkish findings.

Some reports suggested that the simian virus 40 (SV40) could act as a co-carcinogen to induce mesothelioma (Carbone *et al*., 2002). This is a controversial issue; however, this hypothesis can be excluded regarding erionite because SV40 DNA was never found in the specimen of Turkish patients (Emri *et al*., 2000; Carbone *et al*., 2007). Based on the fact that not all exposed villagers died from mesothelioma and that some families in erionite villages seemed to be at particularly high risk, the cause of the high incidence of mesothelioma was hypothetically attributed to the interaction of erionite exposure and genetic factors (Carbone *et al*., 2007). Although it is not possible to exclude some genetic susceptibility, this hypothesis remains largely speculative and is not substantiated by sound data, because all relatives shared the same exposure to erionite since birth, except for some women who came from other villages, and because some mesotheliomas occurred in patients whose parents died from other causes, and vice versa (Bariş & Grandjean, 2006).

2.2 Other cancers

Bariş *et al.* (1996) also studied the cancer-specific mortality in the three Turkish erionite villages of Karain, Tuzköy, and Sarihidir. During 1970–94, 305 deaths were reported in Karain; of these, 177 (58%) were cancers, and included 150 cases (49.2%) of malignant pleural mesothelioma, seven cases (2.3%) of malignant peritoneal mesothelioma, and six (1%) of gastroesophageal carcinoma; four deaths (1.3%) from cancer of the lung included two non-smoking women; there were also three cases (1%) of leukaemia, and six of other malignancies (1.9%). During 1980–94, 519 deaths were reported in Tuzköy and Sarihidir (432 and 87, respectively); of these, 257 were cancers, and included 120 cases of malignant pleural mesothelioma, and 64 cases of malignant peritoneal mesothelioma; 30 patients had "intra-abdominal carcinoma" (according to the authors, some of them might have been peritoneal mesothelioma or ovarian carcinoma), and 14 patients had cancer of the lung (four of whom were non-smoking women); there were five cases of gastroesophageal cancer, five deaths due to leukaemia, and 16 cases of various malignancies including ovarian cancer, mesenchymal tumours, and leiomyosarcoma of the colon. These mortality figures lend some support to the hypothesis that erionite fibres also cause cancer other than mesothelioma and cancer of the lung; however, no statistical comparisons and no mineralogical analyses of the tissues were performed to demonstrate this relationship. Another difficulty is the uncertain validity of diagnoses. Bariş & Grandjean (2006) also looked at other cancers in their follow-up of the inhabitants of Sarihidir and Karain, but the small number of these cancers (*n* = 32, accounting for 9% of the total deaths) precluded a detailed analysis.

2.3 Synthesis

Studies of villages in Turkey where inhabitants were exposed from environmental sources from birth as well as the follow-up of a cohort of emigrants from one of the exposed villages in Sweden showed an extremely high incidence of pleural and peritoneal mesothelioma that can be causally associated with erionite exposure. The potency of erionite to induce mesothelioma seems much higher than for any type of asbestos.

3. Cancer in Experimental Animals

See Section 3 of the *Monograph* on Asbestos in this volume.

4. Other Relevant Data

See Section 4 of the *Monograph* on Asbestos in this volume.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of erionite. Erionite causes mesothelioma.

There is *sufficient evidence* in experimental animals for the carcinogenicity of erionite.

Erionite is *carcinogenic to humans (Group 1).*

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LEATHER DUST

Leather dust was considered by previous IARC Working Groups in 1980 and 1987 (IARC, 1981, 1987). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

Leather is the product obtained by tanning skins and hides by any one of several methods. By convention, the term 'hide' generally refers to the skin-covering of larger animals (cows, steers, horses, buffaloes, etc.), and the term 'skins', to those of smaller animals (calves, sheep, goats, pigs, etc.). Although the physical properties of these different skins vary, their basic chemical, physical, and histological characteristics are similar (IARC, 1981).

1.2 Chemical and physical properties of the agent

The skin is mainly composed of proteins, although it also contains lipids, carbohydrates, inorganic salts, and water. From the point of view of leather manufacture, the proteins of the skin are the most important components. These proteins include collagen (constitutes the bulk of the fibrous portion), and reticulin (similar to collagen, but differing in its ability to combine readily with silver salts). Elastin, also a fibrous protein, is present in very small quantities, mainly in the grain area, and to a small extent in the blood vessels. Most of the non-collagenous proteins are removed during pre-tanning operations, which are effectively a means of preparing a matrix of relatively pure collagen fibres that will subsequently be stabilized by tanning (IARC, 1981).

Tanning is any process that renders animal hides or skins imputrescible without impairing their flexibility after drying. The most commonly used tanning agents have been vegetable tannins, and basic chromium (III) sulfate.

The vegetable tannins fall into two broad chemicals groups: hydrolysable tannins and condensed tannins. Condensed tannins are more complex chemical structures, and are more likely to be found in the bark or wood of a tree, whereas the hydrolysable tannins predominate in the leaves and fruits. Hydrolysable tannins are mainly glucosides (i.e. glucose esterified with polyhydroxyl phenyl carboxylic acids, such as gallic and ellagic acids) that readily ferment to release the free acid used in primitive tanning processes to control acidity. The chemistry of condensed tannins is complex, and they have been identified as oligomers containing 4–10 flavonoid units, each containing 4–6 hydroxyl groups. Molecular weights in non-aqueous solvents range from 1000–3000, although measurements in aqueous

Table 1.1 Leather uses in relation to type of hide or skin

Skin origin	Use
Cow and steer	Shoe and boot uppers, soles, insoles, linings; patent leather; clothing; work gloves; waist belts; luggage and cases; upholstery; transmission belting; sports goods; packings
Calf	Shoe uppers; slippers; handbags; wallets; hat sweatbands; bookbindings
Sheep and lamb	Grain and suede clothing; shoe linings; slippers; dress and work gloves; hat sweatbands; bookbindings; novelties
Goat and kid	Shoe uppers and linings; dress gloves; clothing; handbags
Pig	Shoe suede uppers; dress and work gloves; wallets; fancy leather goods
Deer	Dress gloves; moccasins; clothing
Horse	Shoe uppers; straps; sports goods
Reptile	Shoe uppers; handbags; fancy leather goods

Compiled by the Working Group

solution suggest aggregation or association to give an effective molecular weight of approximately 10000 (IARC, 1981).

In chrome tanning, the trivalent chromium ions form polynuclear complexes involving, typically, four chromium atoms. Ring structures containing coordinated sulfate and hydroxyl ligands are formed, giving an effective ionic weight of approximately 800. When skins are immersed in a solution of basic chromium (III) sulfate, carboxyl side chains on the collagen enter the coordination sphere of the chromium to form an insoluble complex. This reaction, which invariably involves cross-linking, is the basis of chrome tanning (IARC, 1981).

The composition of leather used in the leather-product industries varies. For example, leather used in shoe manufacture may come from the corium part of hide skin processed during tanning. The composition of crust leather varies depending on the tanning processes (Buljan *et al.*, 2000). The reported chromium (III) levels in dust from chrome-tanned leathers have varied from 0.1% to 4.5% by weight (IARC, 1981). Leather may also contain trace amounts of chromium (VI) formed by oxidation of trivalent chromium during the tanning process. For example, in a Danish study of 43 leather products, 35% ($n = 15$) contained chromium (VI) at levels above the detection limit of 3 mg/kg (Hansen *et al.*, 2002).

1.3 Use of the agent

The hides or skins from different animals possess unique physical properties that are inherent to the particular animal or breed of animal, due largely to differences in climate, type of feed, etc., to which the animal is exposed. They are thus used for different specific purposes (Table 1.1). For more detailed descriptions, refer to the previous *IARC Monograph* (IARC, 1981).

1.4 Occupational exposure

For detailed descriptions of historical exposures to leather dust and other agents in the workplace, refer to the previous *IARC Monograph* (IARC, 1981).

1.4.1 Extent of occupational exposure

Leather and leather-product industries have moved gradually from the industrialized countries to the developing world. For example, shoe manufacture in the United States of America decreased by more than 90% during 1965–2002, and the largest footwear exporter to the USA was the People's Republic of China (Markkanen & Levenstein, 2004). China produced 40% of all prepared shoes in the world at the end of the last century (Chen & Chan, 1999), and the

number of employees in shoe manufacture in China was estimated to be about 2 million (Wang *et al.*, 2006). It was reported that Asian countries supply over 80% of the footwear traded in the world market, and the largest production comes from China followed by India, Indonesia, Viet Nam, Thailand, and Pakistan (Vachayil, 2007). In several developing countries, large and medium-sized manufacturers and retailers are known to use subcontracting practices, informal employment, and so-called home-based shoe-making. There are no reliable estimates on the informal workforce, but it is assumed to be even higher than in the formal sector (Markkanen & Levenstein, 2004). According to statistics from the International Labor Organization, other major countries producing leather products were Mexico (n = 302000 employees), Brazil (n = 305000), Indonesia (n = 279000), the Russian Federation (n = 190000), and Italy (n = 168000) (ILO, 2004).

Although several million people are working in the leather and leather-product industries, only a fraction are exposed to leather dust and other air contaminants in the workplace. No worldwide estimates of the numbers of workers exposed were available to the Working Group.

1.4.2 Levels of occupational exposure

Leather dust concentrations in selected studies published since the previous *IARC Monograph* (IARC, 1981) are presented below.

(a) Footwear industry

In a Russian mortality study of 5185 shoe-manufacturing workers employed during 1940–76, Zaridze *et al.* (2001) reported leather dust concentrations in the range of 6.5–12 mg/m^3 in the following production departments: cutting, fitting, lasting and making, and finishing. In this factory, leather dust was present as a co-exposure with solvents and chloroprene.

Shoe repairers are exposed to the dusts generated during scouring. In a Finnish study of shoe repairers from 11 shops, the time-weighted average concentrations of dust were in the range of 0.07–1.0 mg/m^3 in the vicinity of the roughing, scoring, and finishing machines. The dust concentration depended on the age and type of the machine, and the performance of its local exhaust. Electron-microscopic studies showed that the dust samples collected during the machining of shoes contained leather, polymers, and finishing materials. Several degradation products of polymers were present. Dust was formed mainly during the machining of shoes. Dust samples contained also low concentrations of insoluble chromium (0.10–0.32 µg/m^3), and hexavalent chromium (0.01–0.08 µg/m^3) (Uuklainen *et al.*, 2002).

In a Polish study, dust concentrations were higher in shoe-repair shops than in shoe manufacture. In the repair shops, the recorded concentration of inhaled dust fraction was in the range of 0.5 mg/m^3 (glueing of shoes and soles, zipper exchange, and heel abrasion) to 0.9 mg/m^3 (sewing of uppers and scouring of heels), with high short-term (> 1 minute) fluctuations in the range of 0.1–14.6 mg/m^3. In the shoe factories, the mean concentration of inhalable particles (sample duration > 8 hours) was in the range of 0.12–0.91 mg/m^3, but there were high short-term (> 1 minute) fluctuations in the range of 0.62–6.4 mg/m^3 (Stroszejn-Mrowca & Szadkowska-Stańczyk, 2003).

(b) Leather-tanning and -processing industry

Dust is produced during several processes in tanning operations: chemical dust can be produced during the loading of hide-tanning drums; and leather dust impregnated with chemicals is produced during some mechanical operations, including buffing (IARC, 1981). Total dust levels (personal and static) measured in three countries were presented in Table 2 of the previous *IARC Monograph* (IARC, 1981).

Personal levels ranged from a low of 0.1 mg/m³ in buffing to a high of 21 mg/m³ in semi-automatic staking (IARC, 1981).

1.4.3 Particle size distribution

Leather dusts can contain both fibres and grains; the fibres can vary from 30–1200 µm in length and from 10–30 µm in diameter. Grains are usually < 10 µm in diameter. In several surveys in Italy, more than 50% of the total dust in tanneries were reported with having a particle diameter of < 5 µm (IARC, 1981).

Particle sizes have been measured in the dust generated at various workstations in the shoe trade in Poland. The median particle diameter was about 10 µm, and the proportion of extrathoracic particles which would lodge in the nasal fossae was 35–52%, depending on the occupation (Stroszejn-Mrowca & Szadkowska-Stańczyk, 2003).

1.4.4 Exposure to other agents

(a) Footwear industry

Appendices 5 and 6 of the previous *IARC Monograph* list the various chemicals which may occur in the footwear industry. Most are different solvents used in adhesives, lacquers or cleaning agents. They include petroleum hydrocarbons, chlorinated hydrocarbons, ketones, esters, and alcohols (IARC, 1981). Benzene was previously widely used as a solvent in the shoe industry, and exposure levels during that period may have been high. For example, in Italy, the estimated concentrations of benzene in one shoe factory during 1939–65 were in the range of 0–92 ppm (300 mg/m³). The highest exposures occurred in 1954–60, and benzene was banned by legislation in Italy in 1965 (Seniori Costantini *et al.*, 2003).

Wang *et al.* (2006) reviewed 182 articles on benzene exposure in the shoemaking industry in China during 1978–2004. In 1979–2001, 65% of the measurements exceeded the national occupational exposure limit (OEL) of 40 mg/m³ (13 ppm), and 20% of these exceeded 500 mg/m³ (154 ppm). Benzene levels above 1000 mg/m³ (308 ppm) were not uncommon, and some were in excess of 4500 mg/m³ (1385 ppm). It was also reported that, in some cases, pure benzene was used during the 1980s. The national OEL was lowered to 6 mg/m³ (2 ppm) in 2002, but only 24% of the reported measurements in 2002–04 were below the OEL. The average benzene levels in 2002–04 were 25.1 mg/m³ (8 ppm) in fitting uppers with soles, and 73.6 mg/m³ (23 ppm) in the making of soles. The tasks where exposure occurred most often were fitting uppers with soles, soles-making, uppers-embedding, and uppers-making. Benzene-based adhesives are now banned in China and the national standard for benzene in adhesives is regulated to be less than 0.5% (Wang *et al.*, 2006).

At a large shoe factory in Tianjin, China, as part of a cross-sectional study, Vermeulen *et al.* (2006) collected dermal, inhalation, and urine samples (n = 113) from 70 subjects performing representative tasks and operations at the plant. Mean airborne concentrations of benzene and toluene were 1.52 (standard deviation (SD) 2.82) and 7.49 (SD 11.60) ppm, respectively.

Historically, many toluene-based adhesives manufactured in China contained about 10–30% of benzene as impurity (Chen & Chan, 1999). Exposure to other solvents varies widely, but the levels in some factories may be high. For example, in Viet Nam the national OEL of toluene 100 mg/m³ (26 ppm) was exceeded by six times or more in different sections of a shoe-manufacturing plant in 1996. The concentration of acetone was 6–18 times the Vietnamese OEL 200 mg/m³ (84 ppm) (Chen & Chan, 1999).

Leather dust may also contain agents originating from the processing of leather in tanneries. Levels of chromium (VI) compounds in leather dust are usually very low (see Section 1.4.2a). Leather dust may also contain dyes. Dyes which have been used in the boot and shoe

industry include seven dyes classified by IARC in Group 2B (*possibly carcinogenic to humans*): CI Acid Red 114 (CAS, 6459-94-5), auramine (CAS, 492-80-8), benzyl violet 4B (CAS, 1694-09-3), Trypan blue (CAS, 72-57-1), Ponceau MX (CAS, 3761-53-3), Ponceau 3R (CAS, 3564-09-8), and Rosaline (CAS, 632-99-5) in Magenta (IARC, 1981).

Other agents that may or may not have occurred in the footwear industry include salts of chlorophenols (preservative of leather), acrylic resins, isocyanates (reactive primers, two-part adhesives), polyurethanes and other polymers (artificial leather), chloroprene (component of polychloroprene latex), and wood dust (making of wooden shoes and models) (IARC, 1981).

(b) Leather-tanning and -processing industry

Appendices 5 and 6 of Volume 25 list chemicals that may occur in leather tanning (IARC, 1981).

Exposure to chromium (III) salts or vegetable tannins may occur during the weighing and introduction of chromium salts into rotating drums. Also, small amounts of chromium (VI) may be present. Sodium chlorophenates may be used to prevent the deterioration of leather during tanning, and to protect it from mould. Other possible exposures in the tanyard are sulfuric acid and hydrogen sulfide. If dimethylamine is used in the tanning process, *N*-nitrosodimethylamine may be produced (IARC, 1981).

The use of benzidine-based dyes has been reported in the retanning, colouring, and fatliquoring departments of the leather-tanning and –processing industry. A wide array of chemical solvents (e.g. tetrachloroethylene, toluene, xylene, methyl ethyl ketone and isopropanol), pigments, and waxes may be used in the finishing departments. Exposure to formaldehyde may also occur (IARC, 1981).

(c) Other leather-product industries

Exposures in industries producing leather bags, wallets, suitcases, leather-wearing apparel, harnesses, leather furniture and other miscellaneous leather goods are similar to those that occur in the footwear industry (see Section 1.4.2a).

2. Cancer in Humans

The boot and shoe industry was first reviewed in the previous *IARC Monograph* IARC (1981). The then Working Group reviewed the results of case series on cancer of the nasal cavity and paranasal sinuses (referred below as sinonasal cancer), several of which compared the history of exposure among adenocarcinoma cases to other cancer controls. The then *Monograph* Working Group also reviewed the results of case series and case reports of leukaemia, as well as other studies focused on bladder, lymphatic and haematopoietic, oral/pharyngeal, lung, and stomach cancer. The Working Group concluded that "Employment in the boot and shoe industry is causally associated with the development of nasal adenocarcinomas" and that "It is most likely that exposure to leather dust plays a role in the association." The Working Group also concluded that an increased risk for other histological types of nasal cancer "may exist." They also observed that "The occurrence of leukaemia and aplastic anaemia among shoe workers exposed to benzene is well documented." They noted that excesses of bladder cancer were associated with the leather industry, but it was not clear if these could be attributed to shoe workers. They also reported that hypothesis-generating studies had observed excesses associated with cancer of the lung, oral cavity, pharynx, and stomach.

The boot and shoe industry was re-reviewed as part of the previous *IARC Monograph* Supplement 7 (IARC, 1987). In the period

following the publication of Volume 25 several new studies had been published. The Working Group for supplement 7 had access to a new retrospective cohort study, three new proportionate mortality studies, as well as new case–control studies of sinonasal cancer and other cancer sites. The conclusions of the Working Group for Supplement 7 were concordant with those of Volume 25. They also concluded that nasal adenocarcinoma was associated with the boot and shoe industry, and that the highest risk was among those with high exposures to leather dust. They also noted that there was evidence for other types of nasal cancer, and that there was further evidence of an increased risk of leukaemia associated with exposure to benzene in the industry. Mixed evidence that may indicate an excess risk of bladder cancer among shoe workers was also noted. Some associations with lung, oral, pharynx, and stomach cancer as well as kidney cancer and mesothelioma were also observed.

In this *Monograph*, studies published in the time following Supplement 7, as well as others that were not previously considered, are reviewed. Of special note are the retrospective cohort studies. The previously reviewed retrospective cohort study of workers in the boot and shoe industry in three English towns (Pippard & Acheson, 1985) has been updated and the end of follow-up extended to 1991, and the cohort study of Florence shoe workers exposed to benzene (Paci *et al.*, 1989) has also been updated and the follow-up extended to 1991 for a pooled analysis (Fu *et al.*, 1996). A US study of shoe workers focused on exposure to solvents, mostly toluene (Walker *et al.*, 1993), has also been updated (Lehman & Hein, 2006). A Russian study of shoe manufacturing workers focused on exposure to chloroprene has also been published (Bulbulyan *et al.*, 1998). The results of registry-based studies are presented in Table 2.1. Descriptive studies with information based only on death certificates are not included. The methods and results of relevant cohort and related studies are summarized in Table 2.2. Only the most recent results are presented in cases where the cohorts were updated. Also included in Table 2.2 are the methods and results of the previously reported proportionate mortality studies.

The results of relevant case–control studies of sinonasal cancer, including those previously reviewed, are summarized in Table 2.3. Studies of other respiratory cancers are summarized in Table 2.4. Case–control studies of bladder cancer are summarized in Table 2.5. Case–control studies of other cancer sites are summarized in Table 2.6. For case–control studies, only those that assessed the association with boot/shoe workers, the broader category of leather products, or with leather dust are included. Those that explicitly included tannery workers, which have a very different set of exposures, were excluded.

2.1 Sinonasal cancer

An unusual high prevalence of sinonasal cancer among boot and shoe or other leather workers observed in case series from the Northamptonshire region of England first cast suspicion on a possible association between the malignancy and the occupation (Acheson *et al.*, 1970a, b; Acheson, 1976). In the period following the previous *IARC Monograph* Supplement 7, case series continued to report cases of sinonasal cancer among workers that had been employed as shoe workers or exposed to leather dust. For example, Barbieri *et al.* (2005) reported that seven of 100 epithelial sinonasal cancer cases in the Province of Brescia, Italy, were exposed to leather dust with an average latency of 44 years. A large French adenocarcinoma case series reported that 11 of 418 cases had been exposed to leather dust, whereas 353 had been exposed to wood dust (Choussy *et al.*, 2008). [The Working Group noted that even though leather workers are the second most frequently reported group in these sinonasal cancer case series, it is difficult to interpret these results without knowing

Table 2.1 Descriptive and census-based studies

Reference, location, name of study	Population description	Exposure assessment	Organ site (ICD code)	Exposure and histology	No. of cases/deaths	RR* (95%CI) *(unless indicated otherwise)	Adjustment for potential confounders	Comments
Acheson et al. (1970a, b) Incidence study of nasal cancer in Northamptonshire United Kingdom	Comparison of the estimated rate among boot and shoe trade workers (1953–67) to expected numbers based on rates in the Southern Register Areas of England	Occupational history from medical records and mailed survey or interview	Sinonasal cancer, histologically confirmed carcinomas	Boot & shoe workers			Age	
				All types	17	8 [NR]		
				Adenocarcinomas	7	35 [NR]		
				Squamous carcinomas	7	4 [NR]		
Acheson et al. (1981) Incidence study of nasal cancer in England and Wales United Kingdom	1602 cases diagnosed 1963–67 from The Office of Population Censuses and Surveys	Cases were categorized by occupation	Nasal cancer (160, 160.2–160.9)	All leather workers	26	4.4[a]	SIR, adjusted for snuff and tobacco	[a]indicates significance at the 0.01 level
				Shoe makers & repairers	–	7.1[a]		
				Cutters, lasters & sewers	–	4.3[a]		
Acheson et al. (1982) Incidence study of nasal cancer in Northamptonshire United Kingdom	Comparison of the estimated rate among boot and shoe trade workers (1953–67) to expected numbers based on rates in Northamptonshire	Occupational history from medical records & mailed survey or interview	Sinonasal cancer	Male boot & shoe workers			SIR, adjusted for age	
				All types	27	4.8 (3.5–7.9)		
				Adenocarcinomas	11	7.8 (3.7–14.3)		
				Squamous carcinomas	9	3.1 (1.4–5.9)		
				Preparation/finishing	21	4.5 (2.8–6.8)		
Olsen (1988) Pension fund cancer incidence linkage Denmark	382 Cases from the Danish Cancer Registry diagnosed 1970–84. Registry records linked with the Danish supplementary Pension fund	Longest held occupation from Pension Fund	Sinonasal cancer (160.0, 160.2–160.9)	Manufacture of leather products and footwear (except wooden shoes)			SPIR	SPIR for women not provided
				Men	3	12.3 (3.1–33.4)		
				Women	1	0.3 expected		

Table 2.1 (continued)

Reference, location, name of study	Population description	Exposure assessment	Organ site (ICD code)	Exposure and histology	No. of cases/ deaths	RR* (95%CI) *(unless indicated otherwise)	Adjustment for potential confounders	Comments
Andersen *et al.* (1999) Census cancer incidence linkage Nordic countries	Linkage of 1970 Census with incident cancer cases diagnosed in Denmark (1971–87), Finland (1971–90), Norway (1971–91) and Sweden (1971–89)	Leather and shoe workers	All cancers (140–204)	Men employed in the category of shoe and leather workers in the 1970 census	1436	1.1 (1.0–1.1)	SIR, adjusted for age and calendar period	
			Stomach (151)		92	1.0 (0.8–1.3)		
			Colon (153)		107	1.1 (0.9–1.4)		
			Rectum (154)		80	1.1 (0.9–1.4)		
			Nose (160)		11	2.9 (1.5–5.3)		
			Larynx (161)		25	1.1 (0.7–1.6)		
			Lung (162)		264	1.1 (0.9–1.2)		
			Kidney (180.0)		41	0.9 (0.6–1.2)		
			Bladder (181)		114	1.1 (0.9–1.3)		
			Acute leukaemia (204.3)		12	0.9 (0.5–1.6)		
			Other leukaemia (204.0–2, 4)		22	1.0 (0.6–1.5)		
Vasama-Neuvonen et. al. (1999) Census cancer incidence linkage Finland	892591 occupationally active Finnish women at 1970 Census linked with the Finnish Cancer Registry for incidence of ovarian cancer cases during 1971–95	Occupations with proportion exposed ≥ 20% exposure to leather dust using FINJEM	Ovary (183)	No exposure to leather dust		1.0 (ref)	SIR stratified for birth cohort, follow-up period and social status; adjusted for mean number of children, mean age at first birth and turnover rate	Partial overlap with Andersen *et al.* (1999)
				Low (> 0.009 mg/m³)		1.3 (1.0–1.8)		
				Medium/high		no data		
				Occupation:				
				Cutter for footwear	6	2.5 (0.9–5.4)		
				Pattern maker; cutter	27	1.7 (1.1–2.5)		
				Tanner, fellmonger, pelt dresser	3	0.8 (0.2–2.3)		
				Leather sewer	4	0.6 (0.2–1.5)		

Table 2.1 (continued)

Reference, location, name of study	Population description	Exposure assessment	Organ site (ICD code)	Exposure and histology	No. of cases/ deaths	RR* (95%CI) *(unless indicated otherwise)	Adjustment for potential confounders	Comments
Tarvainen *et al.* (2008) Census cancer incidence linkage Finland	All Finns born during 1906–45 (725868 men, 825528 women). Census data linked with the Finnish Cancer Registry 1971–95	Exposure to leather dust using FINJEM	Mouth and pharynx (exluding the nasopharynx) (140–149)	Shoe makers/ cobblers	2	17.4 (2.1–62.9)	SIR, adjusted for age, calendar period and socioeconomic status. Lag time 10 yr	Partial overlap with Andersen *et al.* (1999)
				Leather dust:				
				Low (< 5 mg/ m^3–yr)	5	0.9 (0.3–2.0)		
				Medium (5–19 mg/m^3–yr)	3	1.8 (0.4–5.1)		
				High (20+ mg/ m^3–yr)	0	0.0 (0.0–15.6)		

CI, confidence interval; FINJEM, Finnish job exposure matrix; NR, not reported; RR, relative risk; SIR, standardized incidence ratio; SPIR, standardized proportionate incidence ratio; yr, year or years

Table 2.2 Cohort studies of boot and shoe workers

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure or Sex	Cases/ deaths	RR (95%CI) SMR	Adjustment for potential confounders	Comments
Decouflé & Walrath (1983) USA	Analysis of 3754 deaths (2144 men, 1610 women) among shoe-manufacturing workers identified using union records. Non-whites and persons of unknown sex, race or age were excluded. Deaths were listed from 1966–77 inclusive as obituaries in union newsletters	None	All cancers (140–209)	Men	464	1.10[a]	PMRs calculated from observed and expected deaths adjusted for age and calendar period	[a] indicates statistical significance at the 0.05 level. No sinonasal cancers observed vs 2.2 expected
				Women	430	1.12[a]		
			Oral & pharynx (140–149)	Men (women: $n = 0$)	17	[1.35]		
			Stomach (151)	Men	25	[1.15]		
				Women	19	[1.43]		
			Rectum (154)	Men	22	[1.57[a]]		
				Women	19	[1.81[a]]		
			Liver/gallbladder (155–6)	Men	14	[1.82[a]]		
				Women	17	[2.02[a]]		
			Larynx (161)	Men (women: $n = 1$)	3	[0.48]		
			Lung (162–163)	Men	155	[1.20[a]]		
				Women	35	[0.92]		
			Bladder (188)	Men	11	[0.72]		
				Women	7	[1.37]		
			Kidney (189)	Men	6	[0.61]		
				Women	6	[0.98]		
			Leukaemia (204–207)	Men	20	[1.20]		
				Women	16	[1.24]		
Garabrant & Wegman (1984) Massachusetts USA	Analysis of death certificates of 1962 shoe workers (1195 men, 767 women) who died in Brockton, Haverhill or Peabody (Massachusetts) during 1954–74 identified by indication of an occupation in leather or shoe manufacturing on death certificates	None	All cancers (140–209)	Men	217	1.08	PMRs calculated from observed and expected deaths adjusted for age and calendar period	No sinonasal cancers observed
				Women	131	0.95		
			Oral & pharynx (140–149)	Men (women: $n = 0$)	5	0.93		
			Digestive tract (150–159)	Men	84	1.4 (1.1–1.7)		
				Women	44	0.99		
			Stomach (151)	Men	17	1.49		
				Women	5	0.82		
			Larynx (161)	Men (women: $n = 0$)	3	1.16		
			Lung (162)	Men	55	1.04		
				Women	13	1.07		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure or Sex	Cases/ deaths	RR (95%CI) SMR	Adjustment for potential confounders	Comments
Garabrant & Wegman (1984) (contd.)			Bladder (188)	Men	5	0.56		
				Women	7	2.5 (1.2–5.1)		
			Leukaemia (204)	Men	8	0.95		
				Women	2	0.52		
Walrath *et al.* (1987) New York State USA	Analysis of 4734 death (3512 men, 1222 women) certificates from employees of one shoe-manufacturing company identified using newspaper obituaries. Deaths occurred during 1960–79	None	All cancers (140–209)	Men	689	1.09[a]		[a] indicates statistical significance at the 0.05 level No sinonasal cancers observed vs 1.9 expected
				Women	274	1.08		
			Oral & pharynx (140–149)	Men (women: $n = 1$)	22	1.22		
			Larynx (161)	Men (women: $n = 0$)	7	0.78		
			Lung and pleura (162 163)	Men	163	0.93		
				Women	18	0.84		
			Stomach (151)	Men	71	1.83[a]		
				Women	14	1.28		
			Colon (153)	Men	100	1.53[a]		
				Women	49	1.41[a]		
			Rectum (154)	Men	33	1.42[a]		
				Women	16	1.97[a]		
			Bone (170)	Men (women: $n = 0$)	6	2.23[a]		
			Bladder (188)	Men (women: $n = 1$)	24	0.91		
			Kidney (189)	Men	16	1.16		
				Women	5	1.17		
			Multiple myeloma (203)	Men	10	1.93[a]		
				Women	8	3.46[a]		
			Leukaemia (204–207)	Men	22	0.86		
				Women	7	0.79		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure or Sex	Cases/ deaths	RR (95%CI) SMR	Adjustment for potential confounders	Comments
Fu *et al.* (1996) United Kingdom and Italy	Pooled analysis of 2 updated shoe-manufacturing cohorts. 4215 English (follow-up 1950–91, Pippard & Acheson, 1985) and 2008 Italian (follow-up 1950–90, Paci *et al.*, 1989) shoe workers	Workers classified as exposed to leather dust or solvents based on work history (Italian) or 1939 Census (English)	All causes (001–999)	English cohort	3314	0.8 (0.8–0.8)	SMR, adjusted for sex, age, & calendar period using national rates	High exposure to benzene in the Italian cohort before 1963. Exposure to leather dust in the English cohort in the range of 0.5–7.5 mg/m³ in 1976
				Italian cohort	333	0.9 (0.8–1.0)		
			All cancers (140–208)	English cohort	646	0.8 (0.7–0.8)		
				Italian cohort	127	1.2 (1.0–1.4)		
			Stomach (151)	English cohort	77	0.7 (0.6–0.9)		
				Italian cohort	25	1.9 (1.2–2.8)		
			Colon (153)	English cohort	57	0.9 (0.7–1.2)		
				Italian cohort	10	1.7 (0.8–3.0)		
			Rectum (154)	English cohort	51	1.1 (0.8–1.4)		
				Italian cohort	5	1.4 (0.5–3.3)		
			Pancreas (157)	English cohort	25	0.7 (0.5–1.0)		
				Italian cohort	2	0.5 (0.1–2.0)		
			Nose (160)	English cohort	12	8.1 (4.2–14.1)		
				Probable leather dust	9	11.7 (5.3–22.2)		
				High leather dust	1	25.0 (0.6–139)		
				Probable solvent	2	3.9 (0.5–13.9)		
				High solvent	0	0		
				Italian cohort	1	13.0 (0.31–70.0)		
				Probably leather dust	0	0.0		
				High leather dust	0	0.0		
				Probable solvent	1	20 (0.5–99)		
				High solvent	1	20 (0.5–99)		
			Larynx (161)	English cohort	6	0.7 (0.2–1.4)		
				Italian cohort	2	0.7 (0.1–2.5)		
			Lung (162)	English cohort	186	0.6 (0.5–0.7)		
				Italian cohort	24	1.0 (0.7–1.5)		
			Bone (170)	English cohort	6	2.1 (0.8–4.5)		
				Italian cohort	0	0		
			Bladder (188)	English cohort	34	0.8 (0.6–1.2)		
				Italian cohort	3	0.9 (0.2–2.51)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure or Sex	Cases/ deaths	RR (95%CI) SMR	Adjustment for potential confounders	Comments
Fu *et al.* (1996) (contd.)			Kidney (189)	English cohort	8	0.7 (0.3–1.4)		
				Probable leather dust	5	0.9 (0.3–2.0)		
				High leather dust	1	3.1 (0.1–17.4)		
				Probable solvent	1	0.3 (0.01–1.4)		
				High solvent	0	0		
				Italian cohort	3	2.2 (0.5–6.3)		
				Probable leather dust	0	0 (0–18.5)		
				High leather dust	0	0 (0–92.2)		
				Probable solvent	3	3.5 (0.7–10.3)		
				High solvent	3	4.0 (0.8–11.7)		
			Multiple myeloma (203)	English cohort	7	1.0 (0.4–2.1)		
				Probable solvent	3	1.2 (0.2–3.4)		
				High solvent	1	5.3 (0.1–29.3)		
				Italian cohort	3	3.7 (0.8–10.8)		
				Probable solvent	1	2.2 (0.5–12.1)		
				High solvent	1	2.4 (0.6–13.6)		
			Leukaemia (204–208)	English cohort	14	0.9 (0.5–1.4)		
				Probable solvent	4	0.7 (0.2–1.8)		
				High solvent	0	0 (0–7.9)		
				Italian cohort	7	2.4 (1.0–5.0)		
				Probable solvent	4	2.5 (0.7–6.4)		
				High solvent	4	2.8 (0.8–7.2)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure or Sex	Cases/ deaths	RR (95%CI) SMR	Adjustment for potential confounders	Comments
Bulbulyan *et al.* (1998) Russian Federation	Retrospective study of 5815 Russian shoe-manufacturing workers (4569 women, 616 men) employed for 2 mo during 1940–76, followed from 1979 through 1993. Workers employed in auxiliary departments and management employees were excluded	Exposure categories based on chloroprene industrial hygiene data from 1970s Chloroprene exposure: High, 20 mg/m^3 (with co-exposures of benzene) Medium, 0.4–1 mg/m^3 (with co-exposures of formaldehyde, leather dust) No exposure (with co-exposure of leather dust)	All causes (001–999)	Full cohort	900	1.03 (0.97–1.1)	SMR, adjusted for age and sex using 1992 Moscow rates. RR in dose–response analysis adjusted for sex, age, gender and calendar period	Bladder cancer among men SMR, 2.1 (95%CI: 0.4–6.1) All 5 leukaemia cases in the high chloroprene exposure group employed before 1960 RR, 4.1 (95% CI: 1.1–17), co-exposure to benzene possible
				Any chloroprene	640	1.1 (1.0–1.3)		
				Medium chloroprene	446	1.1 (0.9–1.3)		
				High chloroprene	194	1.2 (1.0–1.5)		
			All cancers (140–208)	Full cohort	265	1.2 (1.1–1.4)		
				Any chloroprene	184	1.0 (0.8–1.3)		
				Medium chloroprene	128	1.0 (0.8–1.4)		
				High chloroprene	56	1.2 (0.9–1.7)		
			Stomach (151)	Full cohort	48	1.2 (0.9–1.6)		
				Any chloroprene	36	1.3 (0.7–2.6)		
				Medium chloroprene	26	1.3 (0.7–2.7)		
				High chloroprene	10	1.3 (0.3–3.1)		
			Colon (153)	Full cohort	21	1.1 (0.7–1.7)		
				Any chloroprene	16	1.4 (0.5–3.8)		
				Medium chloroprene	8	0.9 (0.3–2.8)		
				High chloroprene	8	2.6 (0.8–7.9)		
			Rectum (154)	Full cohort	14	1.1 (0.6–1.9)		
				Any chloroprene	8	0.7 (0.2–2.0)		
				Medium chloroprene	6	0.7 (0.2–2.3)		
				High chloroprene	2	0.5 (0.1–2.7)		
			Liver (155)	Full cohort	10	2.4 (1.1–4.3)		
				Any chloroprene	9	4.2 (0.5–33)		
				Medium chloroprene	6	3.8 (0.5–34)		
				High chloroprene	3	4.9 (0.5–47)		
			Lung (162)	Full cohort	31	1.4 (0.9–2.0)		
				Any chloroprene	23	0.9 (0.4–2.2)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure or Sex	Cases/ deaths	RR (95%CI) SMR	Adjustment for potential confounders	Comments
Bulbulyan *et al.* (1998) (contd.)				Medium chloroprene	18	0.9 (0.4–2.1)		
				High chloroprene	5	1.1 (0.4–3.5)		
			Kidney (189)	Full cohort	10	1.8 (0.9–3.4)		
				Any chloroprene	9	3.8 (0.5–31)		
				Medium chloroprene	7	4.1 (0.5–34)		
				High chloroprene	2	3.3 (0.3–37)		
			Leukaemia (204–208)	Full cohort	13	1.9 (1.0–3.3)		
				Any chloroprene	9	1.1 (0.3–3.7)		
				Medium chloroprene	4	0.7 (0.2–2.7)		
				High chloroprene	5	2.2 (0.6–8.4)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure or Sex	Cases/ deaths	RR (95%CI) SMR	Adjustment for potential confounders	Comments
Lehman & Hein (2006) USA	Update of Walker *et al.* (1993). An SMR analysis of 7828 shoe-manufacturing workers (2545 men, 5283 women) employed for 1 mo or more during 1940–79 at two Ohio manufacturing plants	Exposure data was based on toluene industrial hygiene data from 1970s. Toluene exposure by duration of employment for specific cancers (< 6 mo, 6 mo–1 yr, 2 yr– < 10 yr, > 10 yr)	All causes (0–999)	Men	1367	1.1 (1.0–1.1)	SMR, adjusted for age and calendar period	Results for sinonasal cancer not reported. Reported 'no evidence of any significant level of exposure to leather dust' Reported 'Benzene was not detected in these surveys and company management asserted that benzene had never been present in the solvents used at either of the plants.'
				Women	1768	1.0 (1.0–1.1)		
				Employment:				
				1 mo– < 6 mo	831	1.0 (1.0–1.1)		
				6 mo–2 yr	747	1.0 (1.0–1.1)		
				2 yr– < 10 yr	838	1.1 (1.0–1.2)		
				≥ 10 yr	719	1.0 (1.0–1.1)		
			All cancers (140–208)	Men	314	1.1 (1.0–1.2)		
				Women	482	1.0 (0.9–1.1)		
				Employment:				
				1 mo– < 6 mo	233	1.1 (1.0–1.3)		
				6 mo–2 yr	202	1.1 (0.9–1.2)		
				2 yr– < 10 yr	202	1.0 (0.9–1.2)		
				≥ 10 yr	159	0.9 (0.8–1.1)		
			Buccal cavity & pharynx (140–149)	Men	8	1.1 (0.5–2.2)		
				Women	1	0.2 (0.0–1.0)		
			Stomach (151)	Men	4	0.3 (0.1–0.8)		
				Women	6	0.5 (0.2–1.1)		
			Lung (162)	Men	138	1.4 (1.2–1.7)		
				Women	110	1.3 (1.0–1.5)		
				Employment:				
				1 mo– < 6 mo	75	1.5 (1.2–1.9)		
				6 mo–2 yr	74	1.6 (1.3–2.0)		
				2 yr– < 10 yr	52	1.1 (0.8–1.5)		
				≥ 10 yr	47	1.2 (0.9–1.5)		
			Bladder (188, 189.3–189.9)	Men	9	1.1 (0.5–2.1)		
				Women	6	1.0 (0.4–2.2		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure or Sex	Cases/ deaths	RR (95%CI) SMR	Adjustment for potential confounders	Comments
Lehman & Hein (2006) (contd.)			Kidney (189.0–189.2)	Men	6	0.9 (0.3–1.9)		
				Women	8	1.1 (0.5–2.1)		
			Leukaemia (204–208)	Men	8	0.7 (0.3 –1.4)		
				Women	19	1.2 (0.7–1.9)		
				Employment:				
				1 mo– < 6 mo	8	1.1 (0.5–2.2)		
				6 mo–2 yr	4	0.6 (0.2–1.6)		
				2 yr– < 10 yr	9	1.3 (0.6–2.5)		
				≥ 10 yr	6	1.0 (0.4–2.2)		

CI, confidence interval; mo, month or months; PMR, proportional mortality ratio; RR, relative risk; SMR, standardized mortality ratio; vs, versus; yr, year or years

Table 2.3 Case–control studies on sinonasal cancer in shoe workers or workers exposed to leather dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases/ deaths	OR (95%CI)	Adjustment for potential confounders	Comments
Cecchi *et al.* (1980) Hospital-based Florence, Italy 1963–77	Nose and paranasal sinuses	66 cases (46 men, 20 women) diagnosed with adenocarcinoma in Florence, records from the Otorhinolaryngology clinic and the Radiology Institute of the University of Florence	Controls were matched to cases by sex, age (± 5 yr), place of residence, smoking habits and year of hospital admission. Each case had 2 non-cancer controls admitted to the department of internal medicine in the hospital	Social worker interview to collect data on occupational history	Shoe makers		Adenocarcinomas 7/11 cases 0/22 controls ($P < 0.001$)	Matched on sex, age, place or residence (as surrogate for SES), smoking habits and year of admission	
Hardell *et al.* (1982) Sweden 1970–79	Nose (ICD 160)	44 cases, age 25–85 and residents of Southern Sweden reported to the Swedish Cancer Registry 1970–79	541 controls referents from another study with the same region, 1970–78	Work history from mailed questionnaire	Leather work		1 case (2.8%) vs 5 controls (0.9%)		Case was 1 of 3 adenocarcinomas
Brinton *et al.* (1984) Hospital-based N. Carolina & Virginia, USA 1970–80	Nasal cavity and sinuses (160.0, 160.2–160.5, 160.8–160.9)	193 incident cases from 4 hospitals	2 controls per case matched on age, sex, race, and region. 232 hospital & 140 death certificate controls (deceased cases had 1 living & 1 dead control)	Telephone interview with subject or next-of-kin	Leather or shoe industry Leather exposure		1.3 (0.1–9.4) 0.7 (0.2–2.0)	Adjusted for sex	

Table 2.3 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases/ deaths	OR (95%CI)	Adjustment for potential confounders	Comments
Merler *et al.* (1986) Vigevano, Italy 1968–82	Nasal epithelial tumours Nasal adenocarcinomas	21 cases (16 men, 5 women) from otolaryngology departments of three hospitals, the hospital cancer registry of the National Cancer Institute of Milan and city mortality records	2 controls per case were selected from the general population and matched by vital status, age, sex and residence	Interview to obtain occupational history. Estimated level of exposure based on specific tasks, workplaces, duration, technology and hygienic evaluation			All epithelial tumours:	Matched on age, sex, and residence	Matched and unmatched analyses yielded similar results. Unmatched results presented
					Light/Uncertain	7	7.5 (1.8–31.7)		
					Heavy	11	121 (17.3–844.3)		
							Adenocarcinoma:		
					Light/Uncertain	5	20.4 (2.7–152.0)		
					Heavy	8	88.0 (12.1–642.0)		
Bimbi *et al.* (1988) Hospital-based Milan, Italy 1982–85	Nasal cavity and paranasal sinus (160.0–160.9) (epithelial neoplasms)	53 (40 men, 13 women) cases admitted to the Head and Neck Oncology Department of the National Institute for Study and Treatment of Cancer in Milan	217 controls selected from patients admitted in the same yr with malignant tumour of the nasopharynx, thyroid or salivary glands	Occupational history was taken from hospital records	Leather workers (3 cases, 0 controls)		RR is reported as incalculable because 0 controls reported working in the leather industry		
Loi *et al.* (1989) Hospital-based Pisa, Italy 1972–83	Nasal cavity and paranasal sinus (160.0–160.9)	38 incident cases (all male) of nasal and paranasal sinus cancer admitted to Pisa University Hospital between October 1972 and October 1983	186 hospital controls (5:1 match) matched for sex, age (± 3 yr), province of usual residence, admission date (± 6 mo), excluding nasal tumours, respiratory tract malignancies and lymphomas	Mailed-out questionnaire on employment in leather-working industries & specific occupational risk factors	Leather exposure: All tumours		8.1 (2.0–33.5)	Matched on age, sex, and residence	

Table 2.3 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases/ deaths	OR (95%CI)	Adjustment for potential confounders	Comments
Shimizu et al. (1989) Hospital-based Japan 1983–85	Maxillary sinus (160.2), squamous cell carcinomas only	66 cases aged 42–77 yr (45 men, 21 women) October 1983 to October 1985 six university hospitals in six prefectures	132 controls were randomly selected from the same jurisdiction as the cases residence and matched for age (± 5 yr) and sex (2:1 match)	Self-administered questionnaires, occupational exposures and other risk factors	Leather workers		2.1 (0.1–38.3)	Matched on age and sex	
Bolm-Audorff et al. (1989, 1990) Hospital-based Hessia, Germany 1983–85	Nasal and paranasal sinus cancer (160)	62 cases identified through 85 otorhinolaryngogical and 8 pathology departments	Patients with non-occupational bone fractures matched on age, sex, and residence	In-person interviews	Leather dust exposure		2/62 cases and 0/62 controls	Matched on age, sex, and residence	
Comba et al. (1992a) Hospital-based Verona, Vicenza, Siena, Italy 1982–87	Nasal cavity and paranasal sinus (160) (epithelial neoplasms)	78 cases (55 men, 23 women) from the University of Verona Institute of Pathology and ENT Clinic, ENT departments at the hospitals of Vincenza, Bussolengo, and Legnago and Institute of Pathology at the University of Siena	254 controls (184 men, 70 women) admitted to the same hospitals (excluding chronic rhinosinusal disease and actute nasal bleeding) matched for admission date, hospital, sex, age (± 5 yr) & residence	Interviews and/or mailed questionnaires collected information on occupational history with specific questions for leather workers	Leather workers Shoe makers Associated with leatherwork: Adenocarcinoma Squamous cell carcinoma	5	6.8 (2.2–15) 8.3 (1.9–36) 14.1 (2.6–76) 1.6 (0.21–12)	Matched on age, sex, and residence. 90% confidence limits used	

Table 2.3 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases/ deaths	OR (95%CI)	Adjustment for potential confounders	Comments
Comba *et al.* (1992b) Hospital-based Brescia, Italy 1980–89	Nasal cavity and paranasal sinus (160) (epithelial neoplasms)	35 cases diagnosed and treated by the ENT department of the radiotherapy unit of the Brescia Hospital	102 controls from ENT department and radiotherapy unit files with neoplastic diseases of the head and neck and matched for age (± 5 yr) and sex	Telephone interview to collect detailed occupational history, specific items related to shoe-manufacturing industries	Leather workers (1 case)		9.0	Matched on age and sex	
Magnani *et al.* (1993) Hospital-based Biella, Italy 1976–88	Nasal cavity and paranasal sinus (160.0, 160.2–160.9) (epithelial or unspecified neoplasms)	33 cases identified by the Local Health Authorities of Biella and Cossato	131 controls (4:1 match) randomly chosen and matched on age and sex admitted same hospital, same year	Mailed questionnaire to patient and next-of-kin with work history	Shoe-manufacturing or other leather industries	3	3.5 (0.6–2.-0.3)	Matched on age and sex	
Luce *et al.* (1992, 1993) Population-based France 1986–88	Nasal cavity and paranasal sinus (160.0, 160.2–160.9)	207 (167 men, 40 women) cases of primary malignancies of the nasal cavity and paranasal sinuses diagnosed between January 1986 and February 1988 at 27 hospitals in France	409 controls were obtained from: 1) hospital cancer patients, frequency-matched for age and sex 2) controls selected from lists provided by cases matching for sex, age (± 10 yr), and residence	Physician interview to collect detailed occupational history	Shoe and leather workers: Ever employed < 15 yr > 15 yr 15 yr induction Leather dust: Medium-high level	3 3	Squamous cell carcinomas: 2.1 (0.5–8.3) 1.9 (0.2–18.3) 2.3 (0.4–12.3) 2.1 (0.5–8.3) 3.1 (0.8–12.4) Adenocarcinomas: 0 cases identified	Matched on age and sex	

Table 2.3 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases/ deaths	OR (95%CI)	Adjustment for potential confounders	Comments
Battista *et al.* (1995) Population-based Italy	Nasal cavity and paranasal sinus (160)	96 cases of malignant neoplasms of the nose and paranasal sinuses diagnosed during 1982–87 in the catchment areas of the hospitals of Verona, Vicenza and Siena	378 hospital controls matched for sex, age (± 5 yr), residence and time of admission; all diagnoses were accepted except chronic rhinosinusal disease, acute nasal bleeding	Interviews or mailed questionnaires to collect work history with specific questions in particular industries	Association with occupation:			Matched on age, sex, and residence. 90% confidence limits used	
					Leather workers		6.8 (1.9–25)		
					Shoe makers	2	8.3 (1.9–36)		
Teschke *et al.* (1997) Population-based Canada	Nasal cavity and paranasal sinus (160)	All incident cases with histologically confirmed primary malignant tumours age ≥ 19 yr, 1990–92	Controls were selected randomly from 5-yr age and sex strata of the provincial voters list; frequency-matched for age and sex	Occupational histories were obtained by interview	Shoe and leather workers		0/48 cases and 6/159 controls	Adjusted for age, sex, and smoking	
't Mannetje et al. (1999a) Pooled analysis Italy, France, Netherlands, Germany, Sweden	Nasal cavity and paranasal sinus (160) Adenocarcinomas and squamous cell carcinomas	555 cases (451 men, 104 women)	1705 controls (1464 men, 241 women) from the same studies. The control:case ratio ranged from 1 to 12.3, with an overall ratio of 3.1	Interviews were conducted to collect lifetime occupational histories. Exposures assessed with a job–exposure matrix	Exposure to leather dust:			Adjusted for age, study, sex (when applicable), smoking (when applicable)	The attributable risk for sinonasal cancer in relation to occupation was 33%. Data from Hardell *et al.* (1982), Hayes et al. (1986), Merler *et al.* (1986), Bolm-Audorff et al. (1989), Comba *et al.* (1992a, b), Luce *et al.* (1992) and, Magnani *et al.* (1993)
					Women	7	2.7 (0.8–9.4)		
					Men	26	1.9 (1.1–3.4)		
					Adenocarcinomas	15	3.0 (1.3–6.7)		
					Squamous cell carcinomas	10	1.5 (0.7–3.0)		

CI, confidence interval; OR, odds ratio; RR, relative risk; SES, socioeconomic status; yr, year or years

Table 2.4 Case–control studies on respiratory cancer in shoe workers or workers exposed to leather dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	OR (95%CI)	Adjustment for potential confounders
Gustavsson *et al.* (1998) Community-based Sweden 1988–91	Oral cavity (143–145), pharynx (146–149), larynx (161), oesophagus (150)	545 incident cases (all male) of squamous cell carcinomas taken from the entire population of Swedish men aged 40–79 living in Stockholm or the southern region of Sweden	641 controls (all male) frequency-matched to cases for age and region	Interviewed by nurses on smoking history, use of oral snuff, alcohol habits and occupational history	Leather dust: All sites Oral cavity Pharynx Larynx Oesophagus	 16 3 5 5 3	 2.1 (0.9–4.9) 2.2 (0.5–8.7) 2.8 (0.8–10.2) 2.1 (0.7–6.6) 2.6 (0.6–10.7)	Matched on age and region. Adjusted for alcohol and smoking
Laforest *et al.* (2000) Population-based France 1989–91	Larynx (161) and hypopharynx (148) (squamous cell only)	497 incident (all male) histologically confirmed cases from 15 French hospitals	296 cancer controls from the same medical environment as cases were matched for age and recruited during 1987–91 in the same or nearby hospitals	Occupational physician interview to collect data on lifetime occupational history. Exposures assessed with a job–exposure matrix	Exposure to leather dust: Never exposed Ever exposed Never exposed Ever exposed	 288 8 198 3	Larynx 1.0 0.9 (0.6–1.3) Hypopharynx 1.0 0.8 (0.2–4.1)	Adjusted for age, smoking and alcohol consumption
Jöckel *et al.* (2000) Pooled analysis Germany 1988–93, 1990–96	Lung (162)	4184 (3498 men, 868 women) identified during 1988–93 in Bremen, Frankfurt, and during 1990–96 in North Rhine-Westphalia, Rhineland-Palatinate, East Bavaria, the Saarland, Thuringia, and Saxony	4253 (3541 men, 712 women) population controls matched for sex, age, and region of residence	Interviewed to collect information on job history and occupational exposure	Shoe workers: Men– Ever employed Exposed > 0–3 yr > 3–30 yr > 30 yr Women– Ever employed Exposed > 0–3 yr > 3–30 yr > 30 yr	 63 18 33 12 13 7 6 0	 1.6 (1.0–2.5) 0.7 (0.3–1.4) 2.5 (1.2–5.1) 2.8 (0.9–9.2) 2.7 (0.8–8.8) 3.6 (0.4–32.1) 3.0 (0.6–14.5) no data	Adjusted for smoking and asbestos exposure

Table 2.4 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	OR (95%CI)	Adjustment for potential confounders
Matos *et al.* (2000) Hospital-based Argentina 1994–96	Lung (162)	199 male patients residents in the city or in the province of Buenos Aires and admitted for treatment in any of four hospitals	393 controls; two male control subjects hospitalized for conditions unrelated to tobacco use during the same period and residents in the same area, matched by hospital and age (± 5 yr)	Occupational history obtained by interview; occupational exposure assessed by job–exposure matrix	Occupation: leather shoes & repair	8	1.5 (0.5–4.2)	Adjusted for age group, hospital, pack–year and industries with $P < 0.05$
					Industry: leather shoes & repair	12	2.2 (0.8–5.8)	
Boffetta *et al.* (2003) Pooled analysis France Italy, Spain, Switzerland 1980–83	Larynx (161) and hypopharynx (148)	1010 male cases with histologically confirmed epidermoid carcinomas from Turin, Varese, Pamplona, Calvados, Zaragoza, and Geneva	2176 population-based controls from the same centres, chosen census lists, electoral roles, or population registries	Occupational histories collected by interview	Larynx/ hypopharynx			Adjusted for age, centre, alcohol, and smoking
					Shoe makers/ repair	15	1.2 (0.6–2.6)	
					Shoe finishers	7	3.2 (0.8–13.9)	
					Larynx Only		4.4 (1.0–18.8)	
					Shoe finishers			
					1–10 yr	3	4.6	
					11–20 yr	4	2.7	
					21+ yr	0	0.0	

CI, confidence interval; OR, odds ratio; yr, year or years

Table 2.5 Case–control studies on cancer of the bladder in shoe workers or workers exposed to leather dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	OR (95%CI)	Adjustment for potential confounders	Comments
Cole *et al.* (1972) Population-based Massachusetts, USA 1972	Bladder and lower urinary tract	461 histologically confirmed cases of transitional or squamous cell carcinoma	485 controls selected from the same sex and age from residents lists for the area	Lifetime work history collected by interview	Men: leather products Finishing & associated Contact with finished	79 44 13	2.0 (1.4–2.9) 2.7 (1.6–4.5) 1.7 (0.9–3.4)	Age and smoking	
Silverman *et al.* (1983) Population-based Detroit, USA 1977–78	Bladder and lower urinary tract	303 male, histologically confirmed transitional or squamous cell carcinoma cases identified by 60/61 hospitals in the region	296 controls selected through random-digit dialling or random selection from Health Care Finance Administration lists selected to be similar in age to cases	Lifetime work history collected by interview	Leather & leather products manufacture & repair Shoe repairman and bootblack	4 3	0.5 (0.1–1.6) 0.7 (0.2–3.3)	Unadjusted	
Schoenberg *et al.* (1984) Population-based New Jersey, USA 1978–79	Bladder (188)	658 male, histologically confirmed carcinoma cases	1258 controls selected through random-digit dialling or random selection from Health Care Finance Administration lists selected to be similar in age to cases	Lifetime work history collected by interview	Leather worker Leather products Shoe repair/ bootblack Leather materials	19 6 9 34	1.8 (0.9–3.5) 1.2 (0.4–3.6) 1.9 (0.7–5.1) 1.9 (1.1–3.2)	Age and smoking	

Table 2.5 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	OR (95%CI)	Adjustment for potential confounders	Comments
Marrett *et al.* (1986) Population-based 10 areas, USA 1978–79	Bladder	2982 histologically confirmed carcinoma cases	5782 controls selected through random-digit dialling or random selection from Health Care Finance Administration lists selected to be similar in age to cases	Lifetime work history collected by interview	Leather dust	42	1.4 (0.9–2.1)	Unadjusted	
					< 5 yr	21	1.6 (0.9–2.8)		
					5–14 yr	6	0.8 (0.3–1.9)		
					15+ yr	13	1.4 (0.7–3.0)		
Silverman *et al.* (1989) Population-based 10 areas, USA 1977–78	Bladder	2100 histologically confirmed white male carcinoma cases. 75% of cases were interviewed.	3874 white male controls selected through random-digit dialling (84% interviewed) or random selection from Health Care Finance Administration lists (83% interviewed) selected to be similar in age to cases	Lifetime work history collected by interview	Leather-processing workers	13	1.2 (0.6–2.7)	Smoking	Further adjustment for age, area, education and other factors had no effect
Schumacher *et al.* (1989) Population-based Utah, USA 1977–83	Bladder (188)	417 (332 men and 85 women) cases identified by the Utah cancer registry	877 (685 men and 192 women) controls selected by random-digit dialling or randomly from Health Care Finance Administration lists, frequency-matched on sex and age	Lifetime occupational histories obtained by interview	Men: Ever Leather industry		1.4 (0.5–4.0)	Age, smoking, religion, education	
					< 10 yr		1.4 (0.5–4.6)		
					≥ 10 yr		1.2 (0.1–13.4)		
					> 45 yr before diagnosis		3.0 (0.6–13.8)		
					Men: leather dust	2	0.8 (0.1–5.1)		
					Women: leather dust	1	2.3 (0.03–179)		

Table 2.5 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	OR (95%CI)	Adjustment for potential confounders	Comments
Siemiatycki *et al.* (1994) Population-based case-control study Montreal, Canada 1979–86	Bladder	484 cases among male residents of the Montreal area	1879 cancer cases from the same large study (all sites, excluding kidney) and 533 population controls from random-digit dialling	Extensive interview review by exposure assessment team	Leather workers: < 10 yr ≥ 10 yr Shoe makers: < 10 yr ≥ 10 yr Leather dust: Substantial Non-substantial	 12 14 5 1 8 5	 1.0 (0.5–1.9) 0.7 (0.4–1.3) 2.0 (0.7–5.6) 0.3 (0.0–2.0) 0.7 (0.3–1.5) 0.6 (0.2–1.5)	Age, ethnicity SES, smoking, and coffee consumption	
Teschke *et al.* (1997) Population-based Canada 1990–92	Bladder (188)	All incident cases (n = 105) with histologically confirmed primary malignant tumours age ≥ 19 yr	Controls (n = 139) selected randomly from 5-yr age and sex strata of provincial voters list; frequency-matched for age and sex	Occupational histories were obtained by interview	Shoe and leather workers	2	0.4 (0.1–2.6)	Age, sex, and smoking	
’t Mannetje *et al.* (1999b) Re-analysis of 11 population-based studies Germany, France, Italy, Greece, Denmark, Spain, 1976–96	Bladder	700 incident female cases, age 30–79 yr	2425 population-based or hospital controls individually or frequency-matched on age group and geographic area	Lifetime occupational history	Shoe makers and leather goods makers	7	0.4 (0.2–1.1)	Age, smoking, and study centre	

Table 2.5 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	OR (95%CI)	Adjustment for potential confounders	Comments
Kogevinas *et al.* (2003) Re-analysis of 11 population-based studies Germany, France, Italy, Greece, Denmark, Spain, 1976–96	Bladder	3346 incident male cases, age 30–79 yr	6840 population-based or hospital controls individually or frequency-matched on age group and geographic area	Lifetime occupational history	Leather workers	48	1.3 (0.9–1.9)	Age, smoking, and study centre	Authors reported that risks were higher in studies conducted in 1990s vs 1980s
Samanic *et al.* (2008) Hospital-based Spain 1998–2000	Bladder carcinoma or in situ (1880–1889) (2337)	1219 incident cases (1067 men, 152 women, 84% participation) from 18 hospitals, age 21–80 yr	1465 controls (1105 men, 166 women, 88% participation) from the same hospitals with unrelated diseases and matched on sex, age, race/ethnicity, and hospital	Computer Assisted Interview (CAPI)	Leather, tanning and finishing			Age, region, smoking, other high-risk occupation	
					Overall	28	0.8 (0.4–1.3)		
					< 10 yr	10	0.9 (0.4–2.2)		
					≥ 10 yr	18	0.7 (0.3–1.4)		

CI, confidence interval; OR, odds ratio; yr, year or years; SES, socioeconomic status

Table 2.6 Other case–control studies with results for shoe workers or workers exposed to leather dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	OR (95%CI)	Adjustment for potential confounders	Comments
Mikoczy *et al.* (1996) Nested case–control study Sweden 1900–89	Pancreas, lung, soft tissue sarcoma	68 cases occurred among a cohort of 2487 workers from 3 Swedish tanneries	178 controls, 3 per case, matched on age and selected using incidence-density sampling from the same cohort	Exposure assigned by an occupational hygienist and long-term employees based on work histories	Leather dust:			Age, sex, and plant	All 4 pancreas cases & 1/11 controls exposed to vegetable dust No "noteworthy" associations reported for stomach, kidney, or bladder
					Pancreas	8	7.2 (1.4–35.9)		
					Lung	8	0.7 (0.2–2.1)		
					Soft tissue sarcoma	NR	3.8 (0.3–48.0)		
Costantini *et al.* (2001) Multicentre (12 areas) population-based study Italy 1991–93	Lymphatic and haematopoietic cancers	Incident cases age 20–74 diagnosed during 1991–93. Composed of 811 male and 639 female NHL cases, 193 male and 172 female Hodgkin disease cases, and 383 male and 269 female leukaemia cases	1779 controls randomly selected from the general population frequency-matched on sex and age group	Interview at home to collect detailed occupational history and exposure to solvents and pesticides	Shoe makers and leather goods makers: Men–			Age	Detailed results not presented for women
					NHL and CLL	30	1.0 (0.5–1.9)		
					Hodgkin disease	3	1.2 (0.3–4.0)		
					All leukaemia	7	0.9 (0.3–2.2)		

Table 2.6 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases	OR (95%CI)	Adjustment for potential confounders	Comments
Terry *et al.* (2005) Population-based USA & Canada 1986–89	Leukaemia	811 incident cases from a multisite study	637 controls recruited through random-digit dialling with frequency-matching on age, sex, race, and region	Telephone interview to gather information on employment and duration in 27 occupations	Leather/shoe industry or shoe repair (1+ yr)			Age, sex, race, region, smoking, education, proxy response	Overall 84% response from cases, 34% from proxies. Overall 66% reponse rate with 13% surrogate respondents
					All leukaemia		0.7 (0.3–1.5)		
					AML		0.6 (0.3–1.5)		
Forand (2004) USA 1981–87	Leukaemia (204–208)	36 incident cases during 1981–90 among men 65 yr or older, residing in the town of Union and deceased as of August 1997	144 controls (all men) were matched by death certificate for year of death and year of birth (± 1 yr)	Occupation and employer determined from death certificates	Employment in boot & shoe industry			Matching on date of birth and death	
					AML	13	1.5 (0.7–3.1)		
					Leukaemia	4	1.2 (0.3–4.3)		

AML, acute myeloid leukaemia; CI, confidence interval; CLL, chronic lymphocytic leukaemia; NHL, non-hodgkin leukaemia; NR, not reported; OR, odds ratio; yr, year or years

the prevalence of leather work in the source population.]

Results of descriptive studies from the United Kingdom and the Nordic countries are presented in Table 2.1. High relative risks were observed, particularly when presenting results for adenocarcinoma (Acheson *et al.*, 1970a, 1982). Relative risks in more recent studies are somewhat lower, but still significantly elevated (Acheson *et al.*, 1982; Olsen, 1988; Andersen *et al.*, 1999).

A large excess was reported in the pooled English and Florence cohorts, based on 12 and one cases observed, respectively (Fu *et al.*, 1996). The risk of sinonasal cancer was associated with probable exposure to leather dust in the English cohort (Fu *et al.*, 1996), and the excess was reported to be greatest in the finishing area in the earlier report on the English cohort (Pippard & Acheson, 1985). Results for sinonasal cancer were not reported for the Russian and American shoe-manufacturing cohorts (Bulbulyan *et al.*, 1998; Lehman & Hein, 2006). The US cohort study reported there was 'no evidence of any significant level of exposure to leather dust.' No sinonasal cancer cases were reported in any of the three proportionate mortality ratio (PMR) studies. There were 2.2 and 1.9 expected cases in the studies of Decouflé & Walrath (1983) and Walrath *et al.* (1987), respectively. Expected numbers were not reported for Garabrant & Wegman (1984), see Table 2.2.

Fourteen sinonasal case–control studies and one pooled re-analysis of seven European studies were reviewed. Twelve of the 14 studies observed evidence of an excess of sinonasal cancer, although sometimes based on very small numbers. The largest odds ratios were observed in the Italian studies, with odds ratios in the range of 3.5 (95%CI: 0.6–2.3) (Magnani *et al.*, 1993) to 121 (95%CI: 17.3–844) for heavy leather dust exposure (Merler *et al.*, 1986). In addition, two studies reported an infinite risk (Cecchi *et al.*, 1980 with seven cases and zero controls; Bimbi *et al.*, 1988 with three cases and zero controls). Excesses were also observed in studies from Sweden (Hardell *et al.*, 1982), Japan (Shimizu *et al.*, 1989), Germany (Bolm-Audorff *et al.*, 1989, 1990), and France (Luce *et al.*, 1992, 1993). The only non-positive studies were from the USA (Brinton *et al.*, 1984) and Canada (Teschke *et al.*, 1997), the only North American studies. The pooled re-analysis of European case–control studies observed increased risks associated with leather dust exposure among both men (OR, 1.9; 95%CI: 1.1–3.4) and women (odds ratio [OR], 2.7; 95%CI: 0.8–9.4), see Table 2.3.

Relative risks (RR) for adenocarcinoma were consistently high in descriptive (Acheson *et al.*, 1970b, 1982) and case–control studies (Cecchi *et al.*, 1980; Merler *et al.*, 1986; Comba *et al.*, 1992a; 't Mannetje *et al.*, 1999a). However, smaller excess risks were also observed in the few cases where squamous cell carcinoma results were presented (Shimizu *et al.*, 1989; Luce *et al.*, 1992, 1993; 't Mannetje *et al.*, 1999a).

In reviewing trends from Northamptonshire, the United Kingdom, Acheson *et al.* (1982) noted that the majority of cases had been employed in the departments with the most dusty operations, and that they had much higher risk compared to other operatives (RR, 4.5; 95%CI: 2.8–6.8). The retrospective cohort study of workers employed in the British boot and shoe industry also observed the highest risks among workers employed in the jobs with the highest exposure to leather dust (Pippard & Acheson, 1985). This was also observed in the update of the British cohort for the pooled analysis (Fu *et al.*, 1996). An increased risk among workers with the highest leather dust exposure was also observed in case–control studies that reported results for leather dust exposure (Merler *et al.*, 1986; Luce *et al.*, 2002). Most other case–control studies did not provide details regarding leather dust exposure, although Loi *et al.* (1989) did report that four of five leather workers were milling-machine operators, a group thought to have high leather dust exposure. In a pooled analysis of European

studies 't Mannetje *et al.* (1999a) observed an excess of adenocarcinoma (OR, 3.0; 95%CI: 1.3–6.7) as well as a possible increase for squamous cell carcinoma (OR, 1.5; 95%CI: 0.7–3.0).

2.2 Other respiratory cancers

None of the cohort or PMR studies reported results for the pharynx alone (Table 2.2). Among the three US PMR studies, Decouflé & Walrath (1983) and Walrath *et al.* (1987) observed slightly more cases than expected, but Garabrant & Wegman (1984) observed slightly less cases than expected. Tarvainen *et al.* (2008) observed an excess of oral and pharyngeal cancer among shoe makers in Finland based on only two cases. Gustavsson *et al.* (1998) observed an excess risk of squamous cell cancer associated with leather dust for both oral (OR, 2.2; 95%CI: 0.5–8.7) and pharyngeal (OR, 2.8; 95%CI: 0.8–10.2) cancer. Laforest *et al.* (2000) found no association between exposure to leather dust and squamous cell carcinoma of the hypopharynx. Boffetta *et al.* (2003) did not report separate results for the pharynx, but observed an excess of carcinomas of the larynx and hypopharynx among shoe finishers, but not shoe makers or repairers, see Table 2.4.

No excesses of cancer of the larynx were observed in the updated English or Italian cohorts or the three PMR studies (Table 2.2). Results for cancer of the larynx were not reported in the Russian or US cohorts. Gustavsson *et al.* (1998) observed an excess risk of squamous cell carcinoma of the larynx associated with leather dust exposure (OR, 2.1; 95%CI: 0.7–6.6). Laforest *et al.* (2000) found no association (OR, 0.9; 95%CI: 0.6–1.3) between exposure to leather dust and squamous cell carcinoma of the larynx. Boffetta *et al.* (2003) observed an excess of carcinoma of the larynx among shoe finishers (OR, 4.4; 95%CI: 1.0–18.8) that was not associated with duration of employment.

No excesses of lung cancer were observed in the updated English or Italian cohorts (Fu *et al.*, 1996). An excess was observed among men, but not among women in the Russian cohort (Bulbulyan *et al.*, 1998). The excess was limited to workers exposed to non-solvents who were also identified as having potential exposure to leather dust. An excess of lung cancer among both men and women was observed in the US cohort, which was not related to duration of employment (Lehman & Hein, 2006). Using indirect methods, the authors estimated that part, but not all, of the excess could be due to increased smoking rates among blue-collar workers. Although a small, but significant excess of lung cancer was observed among men (PMR, 1.2; $P < 0.05$) in Decouflé & Walrath (1983), no such excess was observed among women in the same study or among either sex in the other two PMR studies. In a pooled analysis of two German case–control studies, an excess risk for lung cancer among both male and female shoe workers was observed (Jöckel *et al.*, 2000). An excess was also observed in a a small Argentine case–control study (Matos *et al.*, 2000).

2.3 Leukaemia

Early studies reported in the previous *IARC Monograph* identified an unusually high prevalence of leukaemia and aplastic anaemia among shoe workers exposed to benzene in both Italy and Turkey (Aksoy *et al.*, 1974, 1976; Vigliani, 1976; Vigliani & Forni, 1976; Aksoy & Erdem, 1978). An excess was also identified in the Italian cohort study where benzene exposures were reported to be very high until 1963 when regulations were changed (Paci *et al.*, 1989; Fu *et al.*, 1996). An excess of leukaemia was observed among workers in the Russian cohort compared to the general population, and all five were in the highest solvent-exposed group (Bulbulyan *et al.*, 1998). All five of these cases were employed before 1960 when co-exposure to benzene was possible.

No excess was observed in the updated English cohort (Fu *et al.*, 1996). No excess of leukaemia was observed in the US cohort study (Lehman & Hein 2006). However, benzene was not detected in industrial hygiene surveys for the US study and "company management asserted that benzene had never been present in the solvents used at either of the plants." No excesses were observed in the three US PMR studies. Andersen *et al.* (1999) also did not observe an excess in the Nordic Census to tumour registry linkage study. More recent case–control studies, including a large, multicentre Italian study with cases diagnosed during 1991–93, have not observed an excess risk for leukaemia associated with employment in the leather industries (Costantini *et al.*, 2001; Forand, 2004; Terry *et al.*, 2005).

2.4 Cancer of the bladder

An excess of cancer of the bladder was not observed in the updated British, Italian, or US cohorts (Fu *et al.*, 1996; Lehman & Hein, 2006). A significant excess of cancer of the bladder was observed among women shoe workers (PMR, 2; $P < 0.05$) in Decouflé & Walrath (1983). However, no excess was observed among men. No excess of cancer of the bladder among either sex in another PMR study was found (Walrath *et al.*, 1987). Pukkala *et al.* (2009) observed a slight excess in the Nordic Census to tumour registry linkage study (SIR, 1.08; 95%CI: 0.98–1.19).

Results for cancer of the bladder from 11 case–control studies are presented in Table 2.5. Two studies, both using broad definitions of leather work, observed strong evidence of an excess risk. Cole *et al.* (1972) observed an excess risk among leather-product workers. Schoenberg *et al.* (1984) observed an excess among men working with leather materials. Several studies observed very small excesses associated with leather work. Marrett *et al.* (1986) found a very weak association associated with leather dust. Schumacher *et al.* (1989) found very weak evidence of an excess risk associated with the leather industry, but not with leather dust. Kogevinas *et al.* (2003) observed a possible small excess among men from 11 European studies in a pooled re-analysis but 't Mannetje *et al.* (1999b) observed a decreased risk among women from the same studies. Other studies either observed no risk or a decreased risk for cancer of the bladder among leather workers. Silverman *et al.* (1983) did not observe an excess among either leather products workers or shoe repairers in Detroit, USA. Silverman *et al.* (1989) did not observe an excess among either leather processing workers from ten regions of the USA. Siemiatycki *et al.* (1994) and Teschke *et al.* (1997) found no evidence of an association with leather or shoe work. Samanic *et al.* (2008) also did not observe an excess for cancer of the bladder associated with leather industry workers in Spain. [The Working Group noted that the results of Silverman *et al.* (1983) and Marrett *et al.* (1986) were not adjusted for smoking.]

2.5 Other cancers

Excesses of other cancers have been observed in some studies, but no consistent pattern has emerged (Decouflé & Walrath, 1983; Garabrant & Wegman, 1984; Walrath *et al.*, 1987; Mikoczy *et al.*, 1996; Bulbulyan *et al.*, 1998).

2.6 Synthesis

There is consistent and strong evidence from both descriptive and case–control studies associating work in the boot and shoe industry with an increased risk of cancer of the nasal cavity and paranasal sinuses. Among those studies with histological classification of the tumours, very large excess risks were observed for sinonasal adenocarcinoma. When examined in case–control studies, the Brittish cohort study, and case series, this excess appears among workers with the highest leather dust exposure. There

is strong evidence that exposure to leather dust causes cancer of the nasal cavity and paranasal sinuses.

Clusters of leukaemia cases were reported among workers with benzene exposure in the shoe industries of Italy and Turkey in the 1970s. An excess was also observed in an Italian cohort study and among a subgroup of a Russian cohort where benzene exposure was likely to have occurred. A case–control study in Italy did not observe an excess in the industry after changes in industrial practices resulted in large reductions in benzene exposure. Benzene is already recognized as a cause of leukaemia, and is likely to be the explaination of the previous excess observed in the industry.

Several early studies reported an excess risk of bladder cancer among leather workers. Two case–control studies observed an association with the leather industry, but many more recent studies found little or no association with the leather industry when tanning was not considered. For other cancer sites, no consistent pattern of excess risk was observed or too little data was available to adequately assess causality with boot and shoe manufacturing.

3. Cancer in Experimental Animals

No data were available to the Working Group.

4. Other Relevant Data

See Section 4 of the *Monograph* on Wood Dust in this Volume.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of leather dust. Leather dust causes cancer of the nasal cavity and paranasal sinuses.

No data in experimental animals for the carcinogenicity of leather dust were available to the Working Group.

Leather dust is *carcinogenic to humans (Group 1)*.

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SILICA DUST, CRYSTALLINE, IN THE FORM OF QUARTZ OR CRISTOBALITE

Silica was considered by previous IARC Working Groups in 1986, 1987, and 1996 (IARC, 1987a, b, 1997). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

Silica, or silicon dioxide (SiO_2), is a group IV metal oxide, which naturally occurs in both crystalline and amorphous forms (i.e. polymorphic; NTP, 2005). The various forms of crystalline silica are: α-quartz, β-quartz, α-tridymite, β-tridymite, α-cristobalite, β-cristobalite, keatite, coesite, stishovite, and moganite (NIOSH, 2002). The most abundant form of silica is α-quartz, and the term quartz is often used in place of the general term crystalline silica (NIOSH, 2002).

1.1 Identification of the agent

α-Quartz is the thermodynamically stable form of crystalline silica in ambient conditions. The overwhelming majority of natural crystalline silica exists as α-quartz. The other forms exist in a metastable state. The nomenclature used is that of α for a lower-temperature phase, and β for a higher-temperature phase. Other notations exist and the prefixes low- and high- are also used (IARC, 1997). The classification and nomenclature of silica forms are summarized in Table 1.1. For more detailed information, refer to the previous *IARC Monograph* (IARC, 1997).

1.2 Chemical and physical properties of the agent

Selected chemical and physical properties of silica and certain crystalline polymorphs are summarized in Table 1.1. For a detailed discussion of the crystalline structure and morphology of silica particulates, and corresponding physical properties and domains of thermodynamic stability, refer to the previous *IARC Monograph* (IARC, 1997).

1.3 Use of the agent

The physical and chemical properties of silica make it suitable for many uses. Most silica in commercial use is obtained from naturally occurring sources, and is categorized by end-use or industry (IARC, 1997; NTP, 2005). The three predominant commercial silica product categories are: sand and gravel, quartz crystals, and diatomites.

Table 1.1 Nomenclature, CAS numbers, and classification of silica forms with selected physical and chemical properties

Name	CAS No.	Basic Formula	Classification	Synonyms	Properties
Silica	7631-86-9	SiO_2	α-quartz, β-quartz; α-tridymite, β1-tridymite, β2-tridymite; α-cristobalite, β-cristobalite; coesite; stishovite; moganite		Structure: crystalline, amorphous, cryptocrystalline Molecular weight: 60.1 Solubility: poorly soluble in water at 20 °C and most acids; increases with temperature and pH Reactivity: reacts with alkaline aqueous solutions, with hydrofluoric acid (to produce silicon tetrafluoride gas), and catechol
Crystalline Silica					
Cristobalite	14464-46-1		α-cristobalite, β-cristobalite		
Quartz	14808-60-7		α-quartz, β-quartz	α-quartz: agate; chalcedony; chert; flint; jasper; novaculite; quartzite; sandstone; silica sand; tripoli	Solubility: 6–11 µg/cm³ (6–11 ppm) at room temperature; slightly soluble in body fluids Thermodynamic properties: melts to a glass; coefficient of expansion by heat—lowest of any known substance
Tripoli	1317-95-9				
Tridymite	15468-32-3		α-tridymite, β1-tridymite, β2-tridymite		

From IARC, 1997; NIOSH, 2002; NTP, 2005

1.3.1 Sand and gravel

Although silica sand has been used for many different purposes throughout history, its most ancient and principal use has been in the manufacture of glass (e.g. containers, flat plate and window, and fibreglass). Sands are used in ceramics (e.g. pottery, brick, and tile), foundry (e.g. moulding and core, refractory), abrasive (e.g. blasting, scouring cleansers, sawing and sanding), hydraulic fracturing applications, and many other uses. Several uses require the material to be ground (e.g. scouring cleansers, some types of fibreglass, certain foundry applications). In some uses (e.g. sandblasting, abrasives), grinding also occurs during use. For a more complete list of end-uses, refer to Table 8 of the previous *IARC Monograph* (IARC, 1997).

According to the US Geological Survey, world production in 2008 was estimated to be 121 million metric tons (Dolley, 2009). The leading producers were the USA (30.4 million metric tons), Italy (13.8 million metric tons), Germany (8.2 million metric tons), the United Kingdom (5.6 million metric tons), Australia (5.3 million metric tons), France (5 million metric tons), Spain (5 million metric tons), and Japan (4.5 million metric tons).

1.3.2 Quartz crystals

Quartz has been used for several thousand years in jewellery as a gem stone (e.g. amethyst, citrine), and is used extensively in both the electronics and optical components industries. Electronic-grade quartz is used in electronic circuits, and optical-grade quartz is used in windows, and other specialized devices (e.g. lasers) (IARC, 1997).

1.3.3 Diatomites

Diatomites are used in filtration, as fillers (in paint, paper, synthetic rubber goods, laboratory absorbents, anti-caking agents, and scouring powders), and as carriers for pesticides. They impart abrasiveness to polishes, flow and colour qualities to paints, and reinforcement to paper. Other uses include: insulators, absorption agents, scourer in polishes and cleaners, catalyst supports, and packing material (IARC, 1997).

According to the US Geological Survey, world production in 2008 was estimated to be 2.2 million metric tons. The USA accounted for 35% of total world production, followed by the People's Republic of China (20%), Denmark (11%), Japan (5%), Mexico (4%), and France (3%) (Crangle, 2009).

1.4 Environmental occurrence

Keatite, coesite, stishovite, and moganite are rarely found in nature. The most commonly occurring polymorphs are quartz, cristobalite and tridymite, which are found in rocks and soil. These forms of silica can be released to the environment via both natural and anthropogenic sources (e.g. foundry processes, brick and ceramics manufacturing, silicon carbide production, burning of agricultural waste or products, or calcining of diatomaceous earth). Some of these anthropogenic activities may cause transformation of one polymorph into another (NIOSH, 2002).

1.4.1 Natural occurrence

α-Quartz is found in trace to major amounts in most rock types (e.g. igneous, sedimentary, metamorphic, argillaceous), sands, and soils. The average quartz composition of major igneous and sedimentary rocks is summarized in Table 10 of the previous *IARC Monograph* (IARC, 1997). Quartz is a major component of soils, composing 90–95% of all sand and silt fractions in a soil. It is the primary matrix mineral in the metalliferous veins of ore deposits, and can also be found in semiprecious stones, such as amethyst, citrine, smoky quartz, morion, and tiger's eye (IARC, 1997).

Crystalline tridymite and cristobalite are found in acid volcanic rocks. Cristobalite also occurs in some bentonite clays, and as traces in diatomite. Although rarely found in nature, coesite and stishovite have been found in rocks that equilibrated in short-lived high-pressure environments (e.g. meteoritic impact craters), and keatite has been found in high-altitude atmospheric dusts, which are believed to originate from volcanic sources (IARC, 1997).

For a more detailed description of the natural occurrence of crystalline silica and its polymorphs in air, water and soil, refer to the previous *IARC Monograph* (IARC, 1997).

1.5 Human exposure

1.5.1 Exposure of the general population

Inhalation of crystalline silica during the use of commercial products containing quartz is thought to be the primary route of exposure for the non-occupationally exposed (i.e. general) population. Commercial products containing quartz include: cleansers, cosmetics, art clays and glazes, pet litter, talcum powder, caulk, putty, paint, and mortar. No quantitative data on potential levels of exposurem during the use of these products were available at the time of

writing (WHO, 2000). The general population may also be exposed via ingestion of potable water containing quartz particles; however, quantitative data on concentrations of quartz in potable or other forms of drinking-water were again not available (IARC, 1997; WHO, 2000).

1.5.2 Occupational exposure

Because of the extensive natural occurrence of crystalline silica in the earth's crust and the wide uses of the materials in which it is a constituent, workers may be exposed to crystalline silica in a large variety of industries and occupations (IARC, 1997). Table 1.2 lists the main industries and activities in which workers could be exposed to crystalline silica. Included in this table are activities that involve the movement of earth (e.g. mining, farming, construction, quarrying), disturbance of silica-containing products (e.g. demolition of masonry and concrete), handling or use of sand- and other silica-containing products (e.g. foundry processes, such as casting, furnace installation and repair; abrasive blasting; production of glass, ceramics, abrasives, cement, etc.).

Estimates of the number of workers potentially exposed to respirable crystalline silica have been developed by the National Institute of Occupational Safety and Health (NIOSH) in the USA and by CAREX (CARcinogen EXposure) in Europe. Based on the National Occupational Exposure Survey (NOES), conducted during 1981–83, and the *County Business Patterns 1986*, NIOSH estimated that about 1.7 million US workers were potentially exposed to respirable crystalline silica (NIOSH, 2002). Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX database estimates that more than 3.2 million workers in the then 15 Member States of the European Union during 1990–93 were considered as occupationally exposed to respirable crystalline silica above background level (Kauppinen *et al.*, 2000). Nearly 87% of these workers were employed in 'construction' (n = 2080000), 'manufacture of other non-metallic mineral products' (n = 191000), 'other mining' (n = 132000), 'manufacture of pottery, china and earthenware' (n = 96000), 'manufacture of machinery except electrical' (n = 78000), 'iron and steel basic industries' (n = 68000), 'manufacture of fabricated metal products, except machinery and equipment' (n = 68000), and 'metal ore mining' (n = 55000). The countries with the highest number of potentially exposed workers were: Germany (1 million workers), the United Kingdom (580000 workers), Spain (400000 workers), Italy (250000 workers), the Netherlands (170000 workers), France (110000 workers), and Austria (100000 workers) (Kauppinen *et al.*, 2000; Mirabelli & Kauppinen, 2005; Scarselli *et al.*, 2008).

For representative data in the main industries where quantitative exposure levels were available in the published literature and/or where major occupational health studies had been conducted, refer to the previous *IARC Monograph* (IARC, 1997). These main industries include mines and quarries, foundries and other metallurgical operations, ceramics and related industries, construction, granite, crushed stone and related industries, sandblasting of metal surfaces, agriculture, and miscellaneous other operations (IARC, 1997). Data from studies and reviews on crystalline silica exposure published since the previous *IARC Monograph* are summarized below.

(a) Levels of occupational exposure

To estimate the number of US workers potentially exposed to high levels of crystalline silica and to examine trends in exposure over time, Yassin *et al.* (2005) analysed data contained in the OSHA Integrated Management Information System (IMIS) database. After exclusion of duplicate bulk and area samples, a total of 7209 personal sample measurements collected during

Table 1.2 Main activities in which workers may be exposed to crystalline silica

Industry/activity	Specific operation/task	Source material
Agriculture	Ploughing, harvesting, use of machinery	Soil
Mining and related milling operations	Most occupations (underground, surface, mill) and mines (metal and non-metal, coal)	Ores and associated rock
Quarrying and related milling operations	Crushing stone, sand and gravel processing, monumental stone cutting and abrasive blasting, slate work, diatomite calcination	Sandstone, granite, flint, sand, gravel, slate, diatomaceous earth
Construction	Abrasive blasting of structures, buildings Highway and tunnel construction Excavation and earth-moving Masonry, concrete work, demolition	Sand, concrete Rock Soil and rock Concrete, mortar, plaster
Glass, including fibreglass	Raw material processing Refractory installation and repair	Sand, crushed quartz Refractory materials
Cement	Raw materials processing	Clay, sand, limestone, diatomaceous earth
Abrasives	Silicon carbide production Abrasive products fabrication	Sand Tripoli, sandstone
Ceramics, including bricks, tiles, sanitary ware, porcelain, pottery, refractories, vitreous enamels	Mixing, moulding, glaze or enamel spraying, finishing	Clay, shale, flint, sand, quartzite, diatomaceous earth
Iron and steel mills	Refractory preparation and furnace repair	Refractory material
Silicon and ferro-silicon	Raw materials handling	Sand
Foundries (ferrous and non-ferrous)	Casting, shaking out Abrasive blasting, fettling Furnace installation and repair	Sand Sand Refractory material
Metal products including structural metal, machinery, transportation equipment	Abrasive blasting	Sand
Shipbuilding and repair	Abrasive blasting	Sand
Rubber and plastics	Raw material handling	Fillers (tripoli, diatomaceous earth)
Paint	Raw materials handling	Fillers (tripoli, diatomaceous earth, silica flour)
Soaps and cosmetics	Abrasive soaps, scouring powders	Silica flour
Asphalt and roofing felt	Filling and granule application	Sand and aggregate, diatomaceous earth
Agricultural chemicals	Raw material crushing, handling	Phosphate ores and rock
Jewellery	Cutting, grinding, polishing, buffing	Semiprecious gems or stones, abrasives
Dental material	Sandblasting, polishing	Sand, abrasives
Automobile repair	Abrasive blasting	Sand
Boiler scaling	Coal-fired boilers	Ash and concretions

From IARC, 1997

2512 OSHA inspections during 1988–2003 were analysed. The findings suggest that geometric mean crystalline silica exposure levels declined in some high-risk construction industries during the period under study, and revealed a significant decline when compared with silica exposure levels found in a previous study by Stewart & Rice (1990). Geometric mean airborne silica exposure levels among workers in the following industries were significantly lower in 1988–2003

than in 1979–87: general contractor industry (0.057 mg/m³ versus 0.354 mg/m³), bridge-tunnel construction industry (0.069 mg/m³ versus 0.383 mg/m³), and stonework masonry industry (0.065 mg/m³ versus 0.619 mg/m³). Silica exposures in the grey-iron industry also declined by up to 54% for some occupations (e.g. the geometric mean for "furnace operators" in 1979–87 was 0.142 mg/m³ versus 0.066 mg/m³ in 1988–2003). [The Working Group noted that exposure levels may not have decreased globally.]

Table 1.3 presents the more recent studies that assessed the levels of respirable crystalline silica in a range of industries and countries. Other recent exposure studies that did not measure the respirable crystalline silica components are presented below.

(b) Mines

As part of a cohort mortality study follow-up in four tin mines in China, Chen *et al.* (2006) developed quantitative exposure estimates of silica mixed dust. Workers in the original cohort were followed up from the beginning of 1972 to the end of 1994. Cumulative exposure estimates were calculated for each worker using their mine employment records and industrial hygiene measurements of airborne total dust, particle size, and free silica content collected since the 1950s. Total dust concentrations of the main job titles exposed were found to have declined from about 10–25 mg/m³ in the beginning of the 1950s to about 1–4 mg/m³ in the 1980s and 1990s. The respirable fraction of total dust was estimated to be 25 ± 4%, and the respirable crystalline silica concentration was estimated to be 4.3% of the total mixed mine dust

Tse *et al.* (2007) conducted a cross-sectional study to investigate the prevalence of accelerated silicosis among 574 gold miners in Jiangxi, China. Using occupational hygiene data abstracted from government documents and bulk dust data from a study in another gold mine in the region, the estimated mean concentration of respirable silica dust were reported as 89.5 mg/m³ (range, 70.2–108.8 mg/m³). According to government documents, the total dust concentration in underground gold mining was in the range of 102.6–159 mg/m³ (average, 130.8 mg/m³), and the fraction of silica in total dust was around 75.7–76.1%. No data on the proportion of respirable dust were available.

To determine dose–response relationships between exposure to respirable dust and respiratory health outcomes, Naidoo *et al.* (2006) used historical data (*n* = 3645) and current measurements (*n* = 441) to characterize exposure to respirable coal mine dust in three South African coal mines. Jobs were classified into the following exposure zones: face (directly involved with coal extraction), underground backbye (away from the coal mining face), and work on the surface. Based on the 8-hour full-shift samples collected respectively, mean respirable dust concentrations in Mines 1, 2, and 3, were as follows: 0.91 mg/m³ (GSD, 3.39; mean silica content, 2.3%; *n* = 102), 1.28 mg/m³ (GSD, 2.11; mean silica content, 1.4%; *n* = 63), and 1.90 mg/m³ (GSD, 2.23; mean silica content, 2.7%; *n* = 73) at the face; 0.48 mg/m³ (GSD, 2.97; mean silica content, 1.48%; *n* = 30), 0.56 mg/m³ (GSD, 3.71; mean silica content, 1.35%; *n* = 47), and 0.52 mg/m³ (GSD, 4.06; mean silica content, 0.9%; *n* = 41) in the backbye zone; and, 0.31 mg/m³ (GSD, 3.52; mean silica content, 0.95%; *n* = 8), 0.15 mg/m³ (GSD, 3.56; *n* = 6), and 0.24 mg/m³ (GSD, 7.69; mean silica content, 0.64%; *n* = 11) in the surface zone. Based on the historical data, overall geometric mean dust levels were 0.9 mg/m³ (GSD, 4.9), 1.3 mg/m³ (GSD, 3.3), and 0.5 mg/m³ (GSD, 5.6) for Mines 1, 2, and 3, respectively.

(c) Granite-quarrying and -processing, crushed stone, and related industries

Bahrami *et al.* (2008) described the personal exposure to respirable dust and respirable quartz in stone-crushing units located in western Islamic Republic of Iran. A total of 40 personal samples

Table 1.3 Respirable crystalline silica concentrations in various industries worldwide

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m³)	Number of samples	Comments
Mines				
Hayumbu *et al.* (2008), copper mines, the Zambia		Arithmetic mean (SD; range)		Cross-sectional dust exposure assessment; bulk and personal respirable samples; NIOSH method 0600 for gravimetric analysis of respirable dust; NIOSH method 7500 for quartz analysis of bulk and respirable samples; mean personal sampling time: 307 minutes (Mine 1) and 312 minutes (Mine 2)
	Mine 1	0.14 (0.2; 0–1.3)	101	
	Mine 2	0.06 (0.06; 0–0.3)	102	
Weeks & Rose (2006), metal and non-metal mines, USA, 1998–2002		Arithmetic mean (GM)		Mine Safety and Health Administration compliance data from 4726 mines; 8-hour full-shift personal air samples; gravimetric analysis of respirable dust; NIOSH method 7500 for silica analysis; arithmetic and geometric mean exposure calculated and classified by occupation, mine, and state
	Strip and open pit mines	0.047 (0.027)	13702	
	Mills or preparation plants	0.045 (0.027)	1145	
	Underground mines	0.050 (0.029)	1360	
	Overall	0.047 (0.027)	16207	
Bråtveit *et al.* (2003) underground small-scale mining, United Republic of Tanzania, 2001		Geometric mean (GSD)		Personal dust sampling (respirable and total dust) on 3 consecutive day shifts; sampling time varied between 5 and 8 hours; gravimetric analysis of respirable and total dust; NIOSH method 7500 for silica analysis
	Drilling, blasting, and shovelling	2.0 (1.7)	6	
	Shovelling and loading of sacks	1.0 (1.5)	3	
	Overall	1.6 (1.8)	9	
Park *et al.* (2002) diatomaceous earth mining and milling, California, USA, 1942–94	Mines and mills	Arithmetic mean 0.29 Cumulative exposure (mg/m³–yr) 2.16	NR	Re-analysis of data from a cohort of 2342 California diatomaceous earth workers; mean concentration of respirable crystalline silica averaged over years of employment of cohort; crystalline silica content of bulk samples varied from 1–25%, and depended on process location
Mamuya *et al.* (2006) underground coal mining, United Republic of Tanzania; June–August 2003 and July–August 2004		Geometric mean (GSD)		Personal dust samples collected during two periods in 2003 and 2004; 134 respirable dust samples collected and analysed gravimetrically; 125 samples analysed for quartz using NIOSH method 7500
	Development team	0.073 (11.1)	56	
	Mine team	0.013 (2.97)	45	
	Transport team	0.006 (1.84)	11	
	Maintenance team	0.016 (11.05)	13	
	Overall	0.027 (8.18)	125	

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m³)	Number of samples	Comments
Granite-quarrying and -processing, crushed stone, and related industries				
Wickman & Middendorf (2002)		Arithmetic mean (SD)		Exposure assessment surveys in 10 granite sheds to measure compliance; full-shift respirable dust samples in workers' breathing zone and area samples; gravimetric analysis of respirable dust; crystalline silica analysis using OSHA ID 142; TWA exposures calculated
Granite–quarrying, Georgia, USA; May 1993–February 1994	Granite sheds	0.052 (0.047)	40	
Brown & Rushton (2005a) Industrial silica sand, United Kingdom, 1978–2000		Unadjusted geometric mean (GSD)		Samples collected by companies as part of routine monitoring programme; gravimetric analysis; silica content measured by Fourier transform infrared spectrophotometry until 1997 and by X-ray diffraction thereafter; personal and static measurements combined into one data set
	Quarries	0.09 (3.9)	2429 (personal) 583 (static)	
Gottesfeld *et al.* (2008) Stone–crushing mills, India, 2003 (initial phase), 2006 and 2007 (post-implementation of engineering controls)		Arithmetic mean (SD)		Bulk and personal air samples collected; silica analysis using NIOSH method 7500; NIOSH method 0500 for respirable particulates used in 2003
	Prior to water-spray controls (2003)	Cristobalite, 0.09 (0.08)	[5]	
		Quartz, 0.25 (0.12)	[5]	
	After water-spray controls			
	Monsoon season (winter 2007)	Cristobalite, 0.02 (0.01)	[18]	
		Quartz, 0.01 (0.01)	[18]	
	Dry season (summer 2006)	Cristobalite, 0.03 (0.03)	[27]	
		Quartz, 0.06 (0.12(	[27]	
Yingratanasuk *et al.* (2002) Stone carvers, Thailand, 1999–2000		Arithmetic mean	148 (total number of samples)	Cross-sectional study design; full-shift (8-hour) personal dust samples; respirable dust analysed gravimetrically; silica analysis by infrared spectrophotometry
	Carvers (Site 1)	0.22		
	Pestle makers (Site 1)	0.05		
	Mortar makers (Site 2)	0.05		
	Mortar makers (Site 3)	0.88		

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m³)	Number of samples	Comments
Rando *et al.* (2001) Industrial sand industry, North America, 1974–98	Sand-processing plants	Geometic mean 0.042 (overall)	14249	Exposure estimates created for a longitudinal and case-referent analysis of a cohort of industrial sand workers; gravimetric analysis of total dust; silica analysis by X-ray diffraction spectroscopy
Yassin *et al.* (2005) Stonework masonry, USA, 1988–2003	All occupations	Geometric mean (GSD) 0.065 (0.732)	274	Analysis of personal silica measurements ($n = 7209$) in OSHA IMIS; samples collected using OSHA method ID 142 during 2512 compliance inspections
Foundries				
Andersson *et al.* (2009) Iron foundry, Sweden, April 2005–May 2006		Geometric mean (GSD)		Respirable dust, quartz, cristobalite, trydimite samples collected on 2 consecutive workdays for shift and daytime workers; gravimetric analysis conducted using modified NIOSH method; respirable quartz and cristobalite analysed using modified NIOSH method 7500
	Caster	0.020 (1.8)	22	
	Core Maker	0.016 (2.3)	55	
	Fettler	0.041 (2.9)	115	
	Furnace and ladle repair	0.052 (3.7)	33	
	Maintenance	0.021 (2.6)	26	
	Melter	0.022 (2.0)	49	
	Moulder	0.029 (2.6)	64	
	Sand mixer	0.020 (2.3)	14	
	Shake out	0.060 (1.7)	16	
	Transportation	0.017 (2.6)	13	
	Other	0.020 (2.0)	28	
	All occupations	0.028 (2.8)	435	

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m³)	Number of samples	Comments
Yassin *et al.* (2005) Grey–iron foundry, USA 1988–2003		Geometric mean (GSD)		Analysis of personal silica measurements (n = 7 209) in OSHA IMIS; samples collected using OSHA method ID 142 during 2512 compliance inspections
	Spruer	0.154 (0.100)	22	
	Hunter operator	0.093 (1.144)	10	
	Charger	0.091 (0.999)	8	
	Core maker	0.078 (1.033)	89	
	Grinder	0.075 (0.821)	371	
	Molder	0.073 (0.910)	308	
	Abrasive blast operator	0.070 (0.821)	56	
	Sorter	0.067 (0.827)	23	
	Reline cupola	0.067 (0.725)	29	
	Furnace operator	0.066 (0.766)	47	
	Core setter	0.066 (0.671)	23	
	Craneman	0.066 (0.815)	16	
	Cleaning department	0.060 (0.879)	36	
	Inspector	0.057 (1.298)	21	
	Ladle repair	0.055 (0.829)	30	
Other metallurgical operations				
Føreland *et al.* (2008) Silicon carbide industry, Norway, November 2002–December 2003		Geometric mean	720 (total)	Exposure survey conducted in 3 silicon carbide plants; measurements collected to improve previously developed job–exposure matrix; sampling duration close to full shift (6–8 hours); 2 sampling periods of 2 work weeks; gravimetric analysis of respirable dust; silica analysis using modified NIOSH method 7500
	Cleaning operators (Plant A)	0.020 (quartz)		
	Mix operators (Plants A and C), charger/ mix and charger operators (Plant C)	0.008–0.013 (quartz)		
	All other jobs (Plants A, B and C)	< 0.005 (quartz)		
	Charger/mix operators (Plant C)	0.038 (cristobalite)		
Construction				
Tjoe-Nij *et al.* (2003) Construction, the Netherlands		Geometric mean (GSD)		Cross-sectional study design; repeated dust measurements (n = 67) on 34 construction workers; full-shift (6–8 hours) personal respirable dust sampling; gravimetric analysis of respirable dust; silica analysis by infrared spectroscopy (NIOSH method 7602); 8-h TWA concentrations calculated
	Concrete drillers and grinders	0.42 (5.0)	14	
	Tuck pointers	0.35 (2.8)	10	
	Demolition workers	0.14 (2.7)	21	

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m³)	Number of samples	Comments
Akbar-Khanzadeh & Brillhart (2002) Construction, USA		Arithmetic mean (SD)		Task-specific silica exposure assessment conducted as part of an OSHA Consultation Service in Ohio; gravimetric analysis of respirable samples using NIOSH method 0600; silica analysis using in-house method based on NIOSH method 7500 and OSHA ID 142
	Concrete–finishing (grinding)	1.16 (1.36)	49	
Verma *et al.* (2003)		Range (min–max)		Task-based exposure assessment conducted as part of an epidemiological study of Ontario construction workers; personal dust sampling and direct–reading particulate monitoring; gravimetric analysis of respirable dust using modified NIOSH method 0600; respirable silica analysis using modified NIOSH method 7500
	Labourers	0.10–0.15	20	
	Operating engineers	0.04–0.06	3	
	Carpenters, iron workers, masons, painters, terrazzo workers	below detectable limits	17	
Woskie *et al.* (2002) Heavy and highway construction, USA		Geometric mean (GSD)		Personal samples collected using the Construction Occupational Health Program sampling strategy; particulate samples analysed gravimetrically; quartz analysed by Fourier transform infrared spectrophotometry; duration of sampling—6 hours of an 8-hour working day
	Labourers	0.026 (5.9)	146	
	Miscellaneous trade	0.013 (2.8)	26	
	Operating engineers	0.007 (2.8)	88	
Flanagan *et al.* (2003) Construction, USA, August 2000–January 2001		Geometric mean (GSD)		Respirable samples analysed gravimetrically using NIOSH method 0600; silica analysed by Fourier transform infrared spectrophotometry using NIOSH method 7602
	Clean-up, demolition with hand-held tools, concrete cutting, concrete mixing, tuck-point grinding, surface grinding, sacking and patching concrete, and concrete-floor sanding	0.11 (5.21)	113	
Lumens & Spee (2001) Construction, the Netherlands		Geometric mean (GSD)		Personal air samples collected during field study at 30 construction sites; duration of sampling 3 to 4 hours; gravimetric analysis of respirable dust samples; silica analysis using NIOSH method 7500
	Recess miller	0.7 (3.3)	53	
	Demolition worker	1.1 (4.0)	82	
	Inner wall constructor	0.04 (2.6)	36	
	Overall	0.5 (5.6)	171	

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m³)	Number of samples	Comments
Flanagan *et al.* (2006) Construction, USA, 1992–2002		Geometric mean (GSD)		Personal silica measurements collected as part of a silica-monitoring compilation project; data provided by 3 federal or state regulatory agencies (*n* = 827 samples), 6 university or research agencies (*n* = 491), and 4 private consultants or contractors (*n* = 134)
	Abrasive blasters, surface and tuck point grinders, jackhammers, rock drills	0.13 (5.9)	1374	
Akbar-Khanzadeh *et al.* (2007) Construction, USA		Arithmetic mean		Personal samples collected during grinding operations in a controlled field laboratory to evaluate the effectiveness of wet grinding and local exhaust ventilation; samples collected and analysed using NIOSH methods 0600 and 7500
	Uncontrolled conventional grinding	61.7	5 sessions	
	Wet grinding	0.896	7 sessions	
	Local exhaust ventilation grinding	0.155	6 sessions	
Bakke *et al.* (2002) Construction, Norway, 1996–99		Geometric mean (GSD)		Personal samples collected as part of exposure survey; sampling duration: 5 to 8 h; respirable dust analysed gravimetrically; silica analysed by NIOSH method 7500
	Tunnel workers	α-Quartz, 0.035 (5.0)	299	
Linch (2002) Construction, USA, 1992–98		TWA (8-hour)		Personal samples collected as part of NIOSH effort to characterize respirable silica exposure in construction industry; respirable dust collected and analysed according to NIOSH method 0600; silica analysed by NIOSH method 7500
	Abrasive blasting of concrete structures	2.8		
	Drilling concrete highway pavement	3.3		
	Concrete-wall grinding	0.26		
	Concrete sawing	10.0		
	Milling of asphalt	0.36		
Meijer *et al.* (2001) Construction, USA, 1992–93		Arithmetic mean		Personal samples of respirable dust and silica; gravimetric analysis of respirable dust; silica analysed by infrared spectrophotometry
	Concrete workers	0.06	96	
Miscellaneous operations				
Hicks & Yager (2006) Coal-fired power plants, USA		Arithmetic mean		Personal breathing zone samples collected during normal full shifts and analysed by NIOSH method 7500
	Normal production activities	0.048	108	

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of respirable crystalline silica (mg/m³)	Number of samples	Comments
Shih *et al.* (2008) Furnace relining, Taiwan, China		Arithmetic mean		Exposures measured in a municipal waste incinerator during annual furnace relining; respirable dust collected and analysed by NIOSH method 0600; silica analysed by NIOSH method 7500
	Sandblasting	0.578	7	
	Bottom-ash cleaning	0.386	8	
	Wall demolishing	0.116	8	
	Relining	0.041	10	
	Grid repairing	0.042	14	
	Scaffold establishing	0.040	8	
	Others	0.082	8	
Zhuang *et al.* (2001) Pottery factories and metal mines, China, 1988–89		Arithmetic mean		Special exposure survey conducted to compare results obtained from traditional Chinese samplers with nylon cyclones; gravimetric analysis of cyclone samples; silica analysis using X-ray diffraction
	Pottery factories	0.116	54	
	Iron/copper mines	0.017	23	
	Tin mines	0.097	10	
	Tungsten mines	0.101	56	
Yassin *et al.* (2005) Several industries, USA, 1988–2003		Geometric mean (GSD)		Analysis of personal silica measurements (n = 7 209) in OSHA IMIS; samples collected using OSHA method ID 142 during 2512 compliance inspections
	Soap and other detergents	0.102 (0.757)	6	
	Testing laboratories services	0.099 (0.896)	53	
	Cut stone and stone products	0.091 (0.956)	405	
	General contractors	0.091 (0.900)	28	
	Coating engraving	0.075 (0.839)	75	
	Grey–iron foundries	0.073 (0.877)	1 760	
	Concrete work	0.073 (0.705)	94	
	Manufacturing explosives	0.070 (0.841)	9	
	Bridge-tunnel construction	0.070 (0.827)	91	
	Stonework masonry	0.065 (0.732)	274	
	Overall	0.073 (0.919)	7209	

GM, geometric mean; GSD, geometric standard deviation; IMIS, Integrated Management Information System; NIOSH, National Institute for Occupational Safety and Health; NR, not reported; OSHA; SD, standard deviation

and 40 area samples were collected and analysed by X-ray diffraction. Personal samples were collected after the installation of local exhaust ventilation, and area samples were collected inside the industrial units before (*n* = 20) and after (*n* = 20) the installation of local exhaust ventilation. Personal samples were collected from process workers (*n* = 12), hopper workers (*n* = 8), drivers (*n* = 11), and office employees (*n* = 9). Personal concentrations of respirable dust were as follows: process workers, 0.21 mg/m^3; hopper workers, 0.45 mg/m^3; and, drivers, 0.20 mg/m^3. Personal concentrations of respirable quartz were as follows: process workers, 0.19 mg/m^3; hopper workers, 0.40 mg/m^3; and, drivers, 0.17 mg/m^3. Based on the area samples, the average levels of total dust and respirable dust were 9.46 mg/m^3 and 1.24 mg/m^3, respectively. The amount of free silica in the stone was 85–97%.

Golbabaei *et al.* (2004) measured TWA concentrations of total dust, respirable dust, and crystalline silica (α-quartz) in a marble stone quarry located in the north-eastern region of the Islamic Republic of Iran. Full-shift (2 × 4-hour samples) personal breathing zone samples were collected and analysed using gravimetric and X-ray diffraction methods. The highest levels of total and respirable dust exposure were observed for workers in the hammer drill process area (107.9 mg/m^3 and 11.2 mg/m^3, respectively), and the cutting machine workers had the lowest levels of exposure (9.3 mg/m^3 and 1.8 mg/m^3, respectively). The highest concentrations of α-quartz in total and respirable dust were measured in hammer drill process workers (0.670 mg/m^3 and 0.057 mg/m^3, respectively).

In a NIOSH-conducted cohort mortality study of workers from 18 silica sand plants, Sanderson *et al.* (2000) estimated historical quartz exposures using personal respirable quartz measurements (collected during 1974–96) and impinger dust samples (collected in 1946). During 1974–96, a total of 4269 respirable dust samples were collected from workers performing 143 jobs at these 18 plants. Respirable quartz concentrations ranged from less than 1 to 11700 μg/m^3, with a geometric mean concentration of 25.9 μg/m^3. Over one-third of the samples exceeded the Mine Safety and Health Administration permissible exposure limit value for quartz (PEL, 10 mg/m^3/(%quartz + 2)), and half of the samples exceeded the NIOSH recommended exposure limit [at the time] (REL, 0.050 mg/m^3). Quartz concentrations varied significantly by plant, job, and year and decreased over time, with concentrations measured in the 1970s being significantly greater than those measured later.

(d) Foundries

Lee (2009) reported on exposures to benzene and crystalline silica during the inspection of a foundry processing grey and ductile iron. The facility consisted of two buildings: the main foundry where moulding, core-making, metal pouring, and shakeout took place; and, the finishing part of the site where grinding and painting was done. Personal sampling for crystalline silica was conducted in the grinding area, in casting shakeout, and in both the mould- and core-making operations. Eight-hour TWA concentrations of crystalline silica were in the range of 2.11–4.38 mg/m^3 in the grinding area (*n* = 4), 1.18–2.14 mg/m^3 in the shakeout area (*n* = 2), and 1.15–1.63 mg/m^3 in the core-maker area (*n* = 2). The 8-hour TWA concentration in the mould area was 0.988 mg/m^3.

(e) Construction

In a study of cement masons at six commercial building sites in Seattle, WA, USA, Croteau *et al.* (2004) measured personal exposures to respirable dust and crystalline silica during concrete-grinding activities to assess the effectiveness of a commercially available local exhaust ventilation (LEV) system. Levels were measured with and without LEV, one sample directly after the other. A total of 28 paired

samples were collected. The results showed that the application of LEV resulted in a mean exposure reduction of 92%, with the overall geometric mean respirable dust exposure declining from 4.5 to 0.14 mg/m^3. However, approximately one quarter of the samples collected while LEV was being used were greater than the OSHA 8–hour TWA PEL (22% of samples), and the American Conference of Governmental Industrial Hygiene (ACGIH) threshold limit value (26%) for respirable crystalline silica.

Rappaport *et al.* (2003) investigated exposures to respirable dust and crystalline silica among 80 workers in four trades (bricklayers, painters (when abrasive blasting), operating engineers, and labourers) at 36 construction sites in the Eastern and Midwestern USA. A total of 151 personal respirable air samples were collected and analysed using gravimetric and X-ray diffraction methods. Painters had the highest median exposures for respirable dust and silica (13.5 and 1.28 mg/m^3, respectively), followed by labourers (2.46 and 0.350 mg/m^3), bricklayers (2.13 and 3.20 mg/m^3), and operating engineers (0.720 and 0.075 mg/m^3). The following engineering controls and workplace characteristics were found to significantly affect silica exposures: wet dust suppression reduced labourers' exposures by approximately 3-fold; the use of ventilated cabs reduced operating engineers' exposures by approximately 6-fold; and, working indoors resulted in a 4-fold increase in labourers' exposures.

(f) Agriculture

Archer *et al.* (2002) assessed the exposure to respirable silica of 27 farm workers at seven farms in eastern North Carolina, USA. Four-hour personal breathing zone samples (n = 37) were collected during various agricultural activities and analysed for respirable dust, respirable silica, and percentage silica using gravimetric and X-ray diffraction methods. The overall mean respirable dust, respirable silica, and percentage silica values were 1.31 mg/m^3 (n = 37), 0.66 mg/m^3 (n = 34), and 34.4% (n = 34), respectively. The highest respirable dust and respirable silica concentrations were measured during sweet potato transplanting (mean, 7.6 and 3.9 mg/m^3, respectively; n = 5), and during riding on or driving an uncabbed tractor (mean, 3.1 and 1.6 mg/m^3, respectively; n = 13).

Nieuwenhuijsen *et al.* (1999) measured personal exposure to dust, endotoxin, and crystalline silica during various agricultural operations at ten farms in California, USA, between April 1995 and June 1996. A total of 142 personal inhalable samples and 144 personal respirable samples were collected. The highest levels of inhalable dust exposure were measured during machine-harvesting of tree crops and vegetables (GM, 45.1 mg/m^3 and 7.9 mg/m^3, respectively), and during the cleaning of poultry houses (GM, 6.7 mg/m^3). Respirable dust levels were generally low, except for machine-harvesting of tree crops and vegetables (GM, 2.8 mg/m^3 and 0.9 mg/m^3, respectively). The percentage of crystalline silica was higher in the respirable dust samples (overall, 18.6%; range, 4.8–23.0%) than in the inhalable dust samples (overall, 7.4%; range, not detectable to 13.0%).

(g) Miscellaneous operations

Harrison *et al.* (2005) analysed respirable silica dust samples (n = 47) from several Chinese workplaces (three tungsten mines, three tin mines, and nine pottery mines) to determine the effect of surface occlusion by alumino-silicate on silica particles in respirable dust. The average sample percentages of respirable-sized silica particles indicating alumino-silicate occlusion of their surface were: 45% for potteries, 18% for tin mines, and 13% for tungsten mines.

To provide a more precise estimate of the quantitative relationship between crystalline silica and lung cancer, 't Mannetje *et al.* (2002) conducted a pooled analysis of existing quantitative exposure data for ten cohorts exposed to silica

(US diatomaceous earth workers; Finnish and US granite workers; US industrial sand workers; Chinese pottery workers, and tin and tungsten miners; and South African, Australian, and US gold miners). Occupation- and time-specific exposure estimates were either adopted/adapted or developed for each cohort, and converted to milligrams per cubic metre (mg/m^3) respirable crystalline silica. The median of the average cumulative exposure to respirable crystalline silica ranged from 0.04 mg/m^3 for US industrial sand workers to 0.59 mg/m^3 for Finnish granite workers. The cohort-specific median of cumulative exposure ranged from 0.13 mg/m^3–years for US industrial sand workers to 11.37 mg/m^3–years for Australian gold miners.

In a cross-sectional survey, Hai *et al.* (2001) determined the levels of respirable nuisance and silica dusts to which refractory brickworkers were exposed at a company in Ha Noi, Viet Nam. Respirable dust levels were in the range of 2.2–14.4 mg/m^3 at nine sample sites. The estimated free silica content of dust was 3.5% for unfired materials at the powder collectors (n = 8 samples), and 11.4% in the brick-cleaning area following firing (n = 1 sample).

Burgess (1998) investigated processes associated with occupational exposure to respirable crystalline silica in the British pottery industry during 1930–1995, and developed a quantitative job–exposure matrix. Exposure estimates were derived from 1390 air samples, the published literature, and unpublished reports of dust control innovations and process changes. In the matrix, daily 8-hour TWA airborne concentrations of respirable crystalline silica ranged from 0.002 mg/m^3 for pottery-support activities performed in the 1990s to 0.8 mg/m^3 for firing activities in the 1930s. Although exposure estimates within decades varied, median concentrations for all process categories displayed an overall trend towards progressive reduction in exposure during the 65 year span.

2. Cancer in Humans

2.1 Cancer of the lung

In the previous *IARC Monograph* (IARC, 1997) not all studies reviewed demonstrated an excess of cancer of the lung and, given the wide range of populations and exposure circumstances studied, some non-uniformity of results had been expected. However, overall, the epidemiological findings at the time supported an association between cancer of the lung and inhaled crystalline silica (α-quartz and cristobalite) resulting from occupational exposure.

The current evaluation has a primary focus on studies that employed quantitative data on occupational exposures to crystalline silica dust (α-quartz and cristobalite). The establishment of exposure–response relationships not only provides critical evidence of causation, but the availability of quantitative exposures on crystalline silica and other exposures of relevance facilitates the accurate assessment of exposure–response relationships in the presence of potential confounders. In addition to the focus on quantitative exposure–response relationships, a summary of findings from eight published meta-analyses of lung cancer was also elaborated. Of these, the seven meta-analyses involving absolute risk summarize the information from the many studies that did not consider quantitative exposure–response relationships, while the eighth is a meta-analysis of exposure-response.

Findings from cohort studies are given in Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.1.pdf, and those for the case–control studies are provided in Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.2.pdf. Given that there was concern by the previous IARC Working Group that different exposure settings (including the nature of the industry and the crystalline silica polymorph) may give rise to different (or

no) cancer risks, this evaluation is divided into sections based on the industrial setting where exposure to silica occurs. As with other evaluations, data from community-based studies are not included, although studies of persons with silicosis are.

2.1.1 Diatomaceous earth

Work in the diatomaceous earth industry is associated mainly with exposure to cristobalite rather than quartz, and, in the USA, is generally free of other potential confounding exposures apart from exposure to asbestos in a minority of locations. The first study of US diatomaceous earth workers revealed significant positive trends in lung cancer risk with both cumulative exposure to crystalline silica (semiquantitative) and duration of employment (Checkoway *et al.*, 1993). Owing to concerns with confounding from asbestos, estimates of asbestos exposure were developed (Checkoway *et al.*, 1996). Those with uncertain asbestos exposures were omitted from the analysis leading to the loss of seven lung cancer deaths. Among those with no asbestos exposure, the lung cancer standardized mortality ratios (SMR) for the two higher crystalline silica exposure groups were twice the magnitude of those for the two lowest exposure groups, although they were not significantly elevated. Rate ratios, with and without adjustment for asbestos exposure were very similar (within 2%), indicating that confounding due to asbestos was not an issue. Checkoway *et al.* (1997) provided findings from one of the two plants previously investigated but including 7 more years of follow-up as well as newly developed quantitative respirable crystalline silica exposures (Table 2.1 online). The lung cancer relative risks (RR) for the highest unlagged or 15-year exposure category were both significantly elevated. Trends for both unlagged and lagged exposure–response were of borderline significance. Rice *et al.* (2001) used the same cohort to examine risk, assessing the relationship between lung cancer mortality and respirable crystalline silica exposure using a variety of models. All except one model demonstrated statistical significance, and the trends of the predicted rate ratios with cumulative crystalline silica exposure were generally similar across models.

A small cohort study among Icelandic diatomaceous earth workers (Rafnsson & Gunnarsdóttir, 1997) provided findings that supported an effect of crystalline silica on lung cancer risk (SIR, 2.34; 95%CI: 0.48–6.85 for those who had worked 5 or more years). Smoking habits among the workers were reported to be similar to the general population.

2.1.2 Ore mining

Steenland & Brown (1995) updated a cohort of US gold miners previously studied (McDonald *et al.*, 1978; Table 2.1 online). Using quantitative estimates of cumulative exposure based on particle counts, no obvious evidence of exposure–response with lung cancer mortality was observed, nor were any of the exposure category SMRs elevated. In contrast, tuberculosis and silicosis mortality was elevated and exhibited an exposure–response relationship with crystalline silica exposure.

Gold miners were investigated in a South African cohort study (Hnizdo & Sluis-Cremer, 1991) and in case–control studies nested within that cohort study and within another South African gold miner cohort (Reid & Sluis-Cremer, 1996; Tables 2.1 and 2.2 online). In the Hnizdo & Sluis-Cremer, (1991) cohort study, lung cancer mortality was related to cumulative dust exposure when modelled as a continuous variable (respirable-surface-area–years) adjusting for smoking, as well demonstrating a monotonic increase with categories of cumulative exposures. There was also some indication of exposure–response in both case–control studies: RR, 1.12; 95%CI: 0.97–1.3 for Reid & Sluis-Cremer (1996),

and lung cancer mortality was elevated in the highest exposure group adjusting for smoking in the Hnizdo *et al.* (1997) study. [In this study, exposure to uranium did not confound the results.] [The Working Group noted the potential for confounding from radon, and also noted that the South African cohorts might overlap.]

McLaughlin *et al.* (1992) undertook a nested case–control study of lung cancer among the members of a prior cohort study by Chen *et al.* (1992) (Table 2.2 online). The study included workers from iron, copper, tungsten, and tin mines, and used quantitative estimates of crystalline silica dust and certain confounder exposures. Only tin miners showed a clear and substantial exposure–response relationship with the quantitative measures of crystalline silica cumulative exposure. The tin miners underwent further follow-up in a cohort study (Chen *et al.*, 2006) and a nested case–control study (Chen & Chen, 2002). Although the cohort study findings provided some overall indication of elevated lung cancer exposure–response mortality with cumulative dust exposure (Table 2.1 online), the findings were much less clear when presented by mine and silicosis status. In the nested case–control study (Table 2.2 online), there was evidence of exposure–response with cumulative total dust exposures. There was also evidence of a relationship between lung cancer mortality and cumulative arsenic exposure, but the high correlation between arsenic and crystalline silica levels prevented mutual adjustment, and left the etiological factor unclear. The same conclusions, more generally expressed, were reported in a simple ever/never exposed approach by Cocco *et al.* (2001), and were confirmed by Chen *et al.* (2007) adjusting for smoking and other confounding factors. Here, no relationship of lung cancer mortality with cumulative crystalline silica exposure was noted for the tungsten mines, nor was any evidence for the iron and copper mines adjusting for radon. [The Working Group noted that crystalline silica exposures were very low in the iron and copper mines.] For the tin mines, no adjustment for arsenic could be made because of its collinearity with crystalline silica exposure, but in the overall group, adjusting for smoking, arsenic, polyaromatic hydrocarbons (PAHs), and radon, no exposure–response for cumulative crystalline silica exposure emerged either by quintile or through the use of a continuous predictor. This was especially true when the iron/copper mines were removed for reason of having poorer data, when the trend tended towards lower risk with increasing crystalline silica exposure.

Carta *et al.* (2001) examined 724 compensated silicotics with radiographic indication of 1/0 or greater small opacities on the International Labor Organization scale who had worked at Sardinian lead and zinc mines, brown coal mines, and granite quarries. Using quantitative estimates of cumulative exposure to respirable crystalline silica dust and radon, the exposure–response was studied in a cohort study and a nested case–control study of 34 lung cancer cases (Tables 2.1 and 2.2 online). Little evidence of a trend with crystalline silica exposure was observed in either study component (after controlling for smoking, airflow obstruction, radon, and severity of silicosis in the case–control study). A clear relationship emerged with exposure to radon in the case–control study. [The Working Group noted that this study was small.]

2.1.3 Ceramics

A case–control study of Chinese pottery workers showed evidence of elevated risk for lung cancer with exposure to crystalline silica dust, although no obvious exposure–response was seen in the three higher exposure categories (McLaughlin *et al.*, 1992; Table 2.2 online). This study was nested within the cohort analysis by Chen *et al.* (1992). Although reported exposure to asbestos was to be minimal, the workers were exposed to PAHs, and in a separate analysis

there were non-significant elevations in lung cancer risk with increasing cumulative exposure to PAHs. This was confirmed in the follow-up analysis by Chen *et al.* (2007) that found that the pottery workers had the highest PAH levels over all industrial groups. Adjustment for PAHs in the analysis led to the crystalline silica exposure relative risk of 1.1 (95%CI: 1.02–1.12) dropping to 1.0 (95%CI: 0.96–1.09). [The Working Group noted that in the prior analysis of the Chinese ceramics data by McLaughlin *et al.* (1992), adjusting for PAHs slightly raised rather than reduced the crystalline silica exposure relative risks. The correlation between the crystalline silica and PAH exposures was reported as 0.56.]

Another case–control study of pottery workers with quantitative crystalline silica dust exposures was from the United Kingdom (Cherry *et al.*, 1998). This analysis, which was restricted to ever smokers but adjusted for smoking amount and ex-smoking, showed a significantly elevated risk of lung cancer mortality with increasing average intensity of exposure, but not with cumulative exposure. No confounders, apart from smoking, were noted in this report.

Ulm *et al.* (1999) looked at workers in the German ceramics industry, as well as the stone and quarrying industry. The study was based solely on those without silicosis, as assessed using radiographic appearances. No relationship of lung cancer mortality risk with cumulative exposure, average intensity, nor peak exposure was seen in the ceramic worker subset nor overall. [The Working Group noted that the omission of those with silicosis may have restricted the range of crystalline silica exposure in the analysis leading to a loss of power to detect any relationship between crystalline silica exposure and lung cancer mortality. Moreover, the modelling included duration of exposure along with cumulative exposure, perhaps reducing the ability to detect an effect of crystalline silica exposure.]

2.1.4 Quarries

In an extension of the Vermont granite workers study by Costello & Graham (1988), Attfield & Costello (2004) both lengthened the follow-up from 1982 to 1994, and developed and analysed quantitative crystalline silica dust exposures (Table 2.1 online). The exposures were noteworthy for being developed from environmental surveys undertaken throughout the period of the study. However, information on smoking and silicosis status was lacking, although confounding from other workplace exposures was likely to have been minimal or non-existent. The results showed a clear trend of increasing risk of lung cancer mortality with increasing cumulative respirable crystalline silica exposure up until the penultimate exposure group. [The Working Group noted that the findings were heavily dependent on the final exposure group; when it was included, the models were no longer statistically significant.] Graham *et al.* (2004) undertook a parallel analysis of the same data as Attfield & Costello (2004), but did not use quantitative exposures, and adopted essentially the same analytical approach as in their 1998 study. They concluded that there was no evidence that crystalline silica dust exposure was a risk factor for lung cancer, their main argument being that lung cancer risks were similar by duration and tenure between workers hired pre-1940 and post-1940 – periods before and following the imposition of dust controls when the crystalline silica dust levels were very different.

As noted above, Ulm *et al.* (1999) looked at workers in the German stone and quarrying industry (includes some sand and gravel workers), as well as the ceramics industry (Table 2.2 online). The study was based solely on those without silicosis, as assessed using radiographic appearances. Neither cumulative exposure, average intensity, nor peak exposure showed a relationship with lung cancer risk in the stone and quarry worker subset, nor overall. [The Working Group noted

that the omission of those with silicosis may have restricted the range of crystalline silica exposure in the analysis leading to a loss of power to detect any relationship between crystalline silica exposure and lung cancer mortality. Moreover, the modelling included duration of exposure along with cumulative exposure, perhaps reducing the ability to detect an effect of crystalline silica exposure.] Another study of German stone and quarry workers found an excess of lung cancer (SMR, 2.40), but no relationship between lung cancer mortality and crystalline silica exposure. [The Working Group noted that the cohort study included only 440 individuals with 16 lung cancer cases. It was also restricted to those with silicosis, which was likely to lead to a lack of low exposures, a consequent limited exposure range, and low study power.]

Among studies that did not use quantitative estimates of crystalline silica exposure, that by Koskela *et al.* (1994) is of interest because it reported that the workers had little exposure to possible confounding exposures. The risk of lung cancer was significantly elevated among those with longer duration of exposure and longer latency ($P < 0.05$). Guénel *et al.* (1989) also found an excess of lung cancer among stone workers after adjustment for smoking, but this was not the case in a study of slate workers by Mehnert *et al.* (1990).

2.1.5 Sand and gravel

Confounding from other workplace exposures is minimal in sand and gravel operations. There are three main studies of sand and gravel workers, two in North America and one in the United Kingdom. The North American studies appear to arise from the same population of workers although there is no published information on their overlap, if any. Using the basic information from the McDonald *et al.* (2001) cohort study of nine North American sand and gravel workers, Hughes *et al.* (2001) reported significant exposure–response of lung cancer with quantitative estimates of cumulative respirable crystalline silica exposures and other related indices. McDonald *et al.* (2005) examined a slightly smaller subset of the cohort described by McDonald *et al.* (2001) based on an extended update at eight of the nine plants, and also undertook a nested case–control study. Risk of lung cancer increased monotonically with unlagged cumulative exposure ($P = 0.011$), but 15-year lagged cumulative exposures provided a slightly better fit ($P = 0.006$) (Table 2.2 online). These findings were basically similar to those obtained by Hughes *et al.* (2001) using the larger cohort and shorter follow-up time. McDonald *et al.* (2005) reported that average exposure intensity, but not years employed, showed a relationship with lung cancer risk ($P = 0.015$).

Steenland & Sanderson (2001) studied workers in 18 sand and gravel companies in the same trade organization as the nine included in the McDonald *et al.* (2001) study (Table 2.1 online). They, too, employed quantitative estimates of exposure derived from company records, and found indications of a relationship with lung cancer mortality, most strongly in the subset that had worked 6 or more months in the industry ($P < 0.06$). Further analysis using a nested case–control approach found marginal evidence of exposure–response using quartiles of cumulative exposure ($P = 0.04$), but stronger evidence with average intensity ($P = 0.003$). [The Working Group noted that a sensitivity analysis of the effect of smoking in this cohort (Steenland & Greenland, 2004) led to an adjusted overall SMR estimate of 1.43 (95% Monte Carlo limits: 1.15–1.78) compared with the original SMR of 1.60 (95%CI: 1.31–1.93). The analysis did not deal with the exposure–response estimates.]

The mortality experience of crystalline silica sand workers in the United Kingdom was evaluated by Brown & Rushton (2005b). No overall excess of lung cancer was found (although there was a large, and highly significant, variation

in lung cancer SMRs between quarries; range: 0.27–1.61, both extremes $P < 0.01$. Relative risks rose with cumulative respirable crystalline silica dust exposure in the first two quartiles, but fell below 1.0 in the highest quartile, resulting in no trend being detected. [The Working Group noted that Steenland (2005) commented that the low exposures in the Brown & Rushton (2005b) study was likely to have impacted its power to detect a crystalline-silica effect.]

2.1.6 Other industries

Two studies having quantitative exposures to crystalline silica remain, although both industries are known to be associated with exposure to other known or suspected lung carcinogens. The first, by Watkins *et al.* (2002) was a small case–control study focused on asphalt fumes and crystalline silica exposure. Crystalline silica exposures were low compared to most other studies, and there were no significant lung cancer elevations or trends with exposure (Table 2.2 online). The second study was a nested case–control analysis of Chinese iron and steel workers (Xu *et al.*, 1996). A significant trend with cumulative total dust exposure was reported but not for cumulative crystalline silica dust exposure, although the relative risk for the highest crystalline silica-exposed group was elevated. The findings were adjusted for smoking, but not for benzo[*a*]pyrene exposures, for which the relative risks demonstrated a clear and significant trend with cumulative exposure level.

2.1.7 Semiquantitative exposure and expert-opinion studies

The studies that follow used quantitative exposure measurements in deriving crystalline silica exposure estimates for individuals but ultimately converted them to exposure scores or categories in the epidemiological analysis. Hessel *et al.* (1986) undertook a case–control study of lung cancer and cumulative crystalline silica exposure in South African gold miners after coding the dust measurements to four discrete levels (0, 3, 6, 12). No exposure–response was detected. Neither was any evidence of exposure–response detected in the later necropsy study of South African gold miners (Hessel *et al.*, 1990) that used the same approach to code the exposure data. [The Working Group noted that the study methods in the case–control study may have led to overmatching for exposure in the case–control study, and that there may have been some selection bias and exposure misclassification in the second study.]

de Klerk & Musk (1998) undertook a nested case–control analysis of lung cancer within a cohort study of gold miners and showed exposure–response for log of cumulative exposure (exposure-score–years) but not for any other index of exposure. The analysis adjusted for smoking, bronchitis, and nickel exposures, and took account of asbestos exposure. The study by Kauppinen *et al.* (2003) on road pavers found a relative risk for lung cancer of 2.26 in the highest exposure group, but there was no evidence of a linear trend of risk with level of exposure. No adjustment was made for concomitant exposures to PAHs, diesel exhaust, and asbestos, nor smoking. Moulin *et al.* (2000) conducted a nested case–control study to examine lung cancer among workers producing stainless steel and metallic alloys. Their results on 54 cases and 162 controls, adjusted for smoking but not for other confounders, indicated a marginally significant evidence of a trend with increasing crystalline silica exposure as well as with PAH exposure.

Two population-based studies that involved substantial expert opinion in assigning dust levels in developing quantitative crystalline silica exposures Brüske-Hohlfeld *et al.* (2000) and Pukkala *et al.* (2005) showed an increasing risk of lung cancer with increasing crystalline silica exposure after adjustment for smoking, and in the latter study, also for social class and exposure to asbestos.

2.1.8 Pooled analysis, meta-analyses, and other studies

Steenland *et al.* (2001) reported on a case–control analysis nested within a pooled study of data from ten cohorts from a variety of industries and countries (Table 2.2 online). It included information on diatomaceous, granite, industrial sand, and pottery workers, and workers in tungsten, tin, and gold mines. Results from all of the studies had been previously published, although not all had originally employed quantitative estimates of crystalline silica exposure; and for half, the duration of follow-up had been extended. All indices of cumulative crystalline silica exposure (cumulative, unlagged and lagged; log cumulative, unlagged and lagged) showed highly significant trends with lung cancer risk ($P < 0.0001$), and average exposure demonstrated a less significant trend ($P < 0.05$). Of these indices, log cumulative exposure led to homogeneity in findings across the cohorts ($P = 0.08$ and 0.34 for unlagged and 15-year lag respectively). Findings were similar for the mining and non-mining subgroups. No adjustment was made for smoking and other confounders, although it was noted that smoking had previously been shown not to be a major confounder in five of the ten studies. Analyses of subsets of the data omitting cohorts with suspected other confounders (radon in South African gold mines, and arsenic or PAHs in Chinese tin miners and pottery workers) did not change the overall findings. [The Working Group noted that the robustness in the findings to exclusion of cohorts with potential confounders from other occupational exposures indicates that any confounding in the individual studies were unlikely to have had an impact on their findings related to crystalline silica.]

The presence of silicosis in an individual is a biomarker of high exposure to crystalline silica dust. Accordingly, studies of individuals with silicosis have the potential to provide useful information on the lung cancer risk associated with exposure to crystalline silica. Three meta-analyses have focused on the risk of lung cancer among individuals with silicosis (Smith *et al.*, 1995; Tsuda *et al.*, 1997; Lacasse *et al.*, 2005). Erren *et al.* (2009) also provide summary information in an electronic supplement to their article. Four others have looked at crystalline silica exposure (including silicosis status unknown and those without silicosis; Steenland & Stayner, 1997; Kurihara & Wada, 2004; Pelucchi *et al.*, 2006; Erren *et al.*, 2009). The number of studies included ranged from 11 in a meta-analysis focused on individuals without silicosis (Erren *et al.*, 2009) to 43 (Pelucchi *et al.*, 2006) in a study of those with and without silicosis. Reasons for this variation included: the publication date, the time period of interest, whether the study was focused on those with or without silicosis, the originating country of the studies, and analysis-specific criteria. For example, Steenland & Stayner (1997) rejected studies of miners and foundry workers on the assumption that they had the greatest potential for confounding exposures, and Smith *et al.* (1995) rejected certain studies they deemed under or overestimated the risk of lung cancer. Overall, of the total of 112 publications included by one or more of the seven meta-analyses, none were common to all analyses.

The detailed results from the seven meta-analyses are shown in Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.3.pdf. In brief, all analyses except for those devoted to categories without silicosis found an elevated lung cancer risk, whether occurring among those with silicosis or among crystalline-silica-exposed workers, or arising from cohort or case–control studies. [The Working Group noted that studies that restrict their analysis to individuals without silicosis potentially limit their range of crystalline silica exposure, because individuals with the highest exposures tend to be omitted. Limiting the range of exposure results in reduced power to detect associations.] Overall, the rate ratios were

very similar across studies (1.74–2.76 for those with silicosis, and 1.25–1.32 for workers exposed to crystalline silica). Results from case–control studies, where there is greater opportunity to control for smoking, revealed lower rate ratios than from cohort studies in two analyses, greater rate ratios in two, and about the same in the fifth (the sixth analysis did not break the results out separately by study type). Moreover, the supplementary materials of Erren *et al.* (2009) show equal risk for crystalline silica exposure in unadjusted and smoking-adjusted studies. The two available analyses providing results on workers exposed to crystalline silica by type of study reported larger rate ratios from the case–control studies.

A further meta-analysis examined exposure–response (Lacasse *et al.*, 2009) rather than overall risk, and for this reason its findings are reported separately. The analysis included findings from ten studies having quantitative measurements of crystalline silica exposure and adjustment for smoking. An increasing risk of lung cancer was observed with increasing cumulative exposure to crystalline silica above a threshold of 1.84 mg/m^3 per year. Although the overall findings were heterogeneous, they were similar to those from a subset of seven more homogeneous studies.

Many of the meta-analyses noted that a lung cancer risk was apparent either after adjusting for smoking or among non-smokers (Smith *et al.*, 1995; Tsuda *et al.*, 1997; Kurihara & Wada, 2004; Lacasse *et al.*, 2005). Yu & Tse (2007) further explored the issue of smoking on the interpretation of the published cohort and case–control studies of crystalline silica exposure and lung cancer. In this, they examined reported SMRs and standardized incidence ratios (SIR) for lung cancer reported in ten different published studies, and concluded that the risk had been systematically underreported for never smokers. After adjustment, five of the ten SMRs and SIRs showed significant lung cancer excesses among never smokers compared to two when unadjusted, and ranged from 2.60–11.93. The SMRs and SIRs for ever smokers were reduced after adjustment for smoking, but tended to retain their statistical significance.

2.2 Other cancers

2.2.1 Cancer of the stomach

In the 40 reports with information on cancer of the stomach, 18 had relative risks > 1.0 (including three significantly elevated), and 22 with relatives risks ≤ 1.0 (including two significantly reduced).

2.2.2 Digestive, gastro-intestinal, or intestinal cancers

In the 15 reports of digestive, gastro-intestinal, or intestinal cancer, seven had relative risks > 1.0 (including one significantly elevated), and eight with reltaive risks ≤ 1.0 (two significantly reduced).

2.2.3 Cancer of the oesophagus

In the 14 reports of oesophageal cancer, five had relative risks > 1.0 (including three significantly elevated), and nine with relative risks ≤ 1.0.

Wernli *et al.* (2006) reported a hazard ratio of 15.80 (95%CI: 3.5–70.6) among Chinese textile workers exposed for over 10 years to crystalline silica dust. In Chinese refractory brick workers, Pan *et al.* (1999) found not only a significant elevation with being ever exposed to crystalline silica dust (RR, 2.75; 95%CI: 1.44–5.25), but also a clear exposure–response relationship with years of exposure, adjusting for smoking and other personal factors. [The Working Group noted that confounding from exposure to PAHs could not be ruled out in the above two studies.]

Yu *et al.* (2007) reported an overall SMR for cancer of the oesophagus of 2.22 (95%CI: 1.36–3.43), and an SMR of 4.21 (95%CI: 1.81–8.30)

among caisson workers (who were noted to have had higher exposures to crystalline silica dust than non-caisson workers). The relative risk of oesophageal cancer for caisson workers with silicosis was reduced to 2.34 after adjusting for smoking and alcohol drinking. No excess risk of oesophageal cancer was observed among the non-caisson workers with silicosis after adjustment.

2.2.4 Cancer of the kidney

In the eight reports on cancer of the kidney, five had relative risks > 1.0 (including two significantly elevated), and three with relative risks ≤ 1.0. The two with significantly elevated risks provided information on exposure–response relationships with crystalline silica exposure, although neither formally evaluated this. In US sand and gravel workers (McDonald *et al.*, 2005), a non-significant negative trend with increasing crystalline silica exposure was observed. However, in Vermont granite workers (Attfield & Costello, 2004), kidney cancer SMRs increased almost monotonically with increasing exposure (except for the last exposure group), and the SMR of 3.12 in the penultimate exposure group was significantly elevated.

2.2.5 Others

There have been isolated reports of excesses in other cancers but the evidence is, in general, too sparse for evaluation. Elci *et al.* (2002) reported an excess of cancer of the larynx in workers potentially exposed to crystalline silica dust, particularly for supraglottic cancer (OR, 1.8; 95%CI: 1.3–2.3), with a significant exposure–response relationship.

2.3 Synthesis

Findings of relevance to lung cancer and crystalline silica exposure arise from five main industrial settings: ceramics, diatomaceous earth, ore mining, quarries, and sand and gravel. Of these, the industries with the least potential for confounding are sand and gravel operations, quarries, and diatomaceous earth facilities. Among those industry segments, most studies with quantitative exposures report associations between crystalline silica exposure and lung cancer risk. The findings are supported by studies in these industries that lack quantitative exposures. Results from the other industry segments generally added support although some studies had potential confounding from arsenic, radon, or PAHs. In one case among Chinese tin miners, the arsenic and crystalline silica exposures were virtually collinear, and no adjustment could be made for arsenic. In another (Chinese pottery workers), adjustment for PAHs removed a significant crystalline silica exposure effect, and in a third, among iron and copper miners, the crystalline silica effect disappeared after adjustment for radon. In these, the role of crystalline silica exposure must be regarded as unclear. Mixed findings were reported among gold, tungsten, and lead/zinc miners.

The strongest evidence supporting the carcinogenicity of crystalline silica in the lung comes from the pooled and meta-analyses. The pooled analysis demonstrated clear exposure–response, while all of the meta-analyses strongly confirmed an overall effect of crystalline silica dust exposure despite their reliance on different studies in coming to their conclusions.

Cancers other than that of the lung have not been as thoroughly researched. In many cases the findings were reported in passing, in analyses focused on lung cancer, and rarely have the data examined exposure–response with crystalline silica exposure or its surrogates.

3. Cancer in Experimental Animals

No additional relevant cancer bioassays have been conducted since the previous *IARC Monograph* (IARC, 1997) except for a study in hamsters by inhalation (Muhle *et al.*, 1998), and a study in mice by intratracheal instillation (Ishihara *et al.*, 2002). Studies from the previous evaluation considered adequate are summarized below together with the new studies published since.

3.1 Inhalation exposure

See Table 3.1

3.1.1 Mouse

Female BALB/cBYJ mice exposed to crystalline silica by inhalation (Wilson *et al.*, 1986) did not have an increase in lung tumours compared to controls. Pulmonary adenomas were observed in both the silica-exposed (9/60) and the control animals (7/59). [The Working Group noted that the study groups were small (6–16 mice).]

3.1.2 Rat

Male and female F344 rats were exposed to 0 or 52 mg/m^3 of crystalline silica (Min-U-Sil) over a 24-month period. Interim removals of ten males and ten females per group were made after 4, 8, 12, and 16 months of exposure. Half of those removed were necropsied, and half were held until the end of the 24 months. None of the controls developed a lung tumour. In the silica-exposed rats, the first pulmonary tumour appeared at 494 days, and the incidence was 10/53 in females and 1/47 in males (Dagle *et al.*, 1986).

One group of 62 female F344 rats was exposed by nose-only inhalation to 12 mg/m^3 crystalline silica (Min-U-Sil) for 83 weeks. An equal number of controls was sham-exposed to filtered air, and 15 rats were left untreated. The animals were observed for the duration of their lifespan. There were no lung tumours in the sham-exposed group, and 1/15 unexposed rats had an adenoma of the lung. In the quartz-exposed rats, the incidence of lung tumours was 18/60 (Holland *et al.*, 1983, 1986; Johnson *et al.*, 1987).

Groups of 50 male and 50 female viral antibody-free SPF F344 rats were exposed by inhalation to 0 or 1 mg/m^3 silica (DQ12; 87% crystallinity as quartz) for 24 months. The rats were then held for another 6 weeks without exposure. The incidence of lung tumours in the silica-exposed rats was 7/50 males and 12/50 in females. Only 3/100 controls had lung tumours (Muhle *et al.*, 1989, 1991, 1995).

Three groups of 90 female Wistar rats, 6–8 weeks old, were exposed by nose-only inhalation to 6.1 or 30.6 mg/m^3 DQ12 quartz for 29 days. Interim sacrifices were made immediately after the exposure and at 6, 12, and 24 months, with the final sacrifice at 34 months after exposure. The total animals with lung tumours was 0 (controls), 37/82 (low dose), and 43/82 (high dose). Many animals had multiple tumours (Spiethoff *et al.*, 1992).

3.1.3 Hamster

Groups of 50 male and 50 female Syrian golden hamsters were exposed to 0 (control) or 3 mg/m^3 DQ12 quartz (mass median aerodynamic diameter, 1.3 µm) for 18 months. The experiment was terminated 5 months later. In the silica-exposed group, 91% of the animals developed very slight to slight fibrosis in the lung, but no significant increase of lung tumours was observed (Muhle *et al.*, 1998)

Table 3.1 Studies of cancer in experimental animals exposed to crystalline silica (inhalation exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start Particle size, GSD	Incidence of tumours in respiratory tract	Significance	Comments
Mouse, BALB/c BYJ (F) 150, 300 or 570 d Wilson *et al.* (1986)	0, 1.5, 1.8 or 2.0 mg/m^3 8 h/d, 5 d/wk 6–16 animals Diameter < 2.1 µm	Lung (adenomas): 7/59 (control), 9/60 (all exposed)	[NS]	
Rat, F344 (M, F) 24 mo Dagle *et al.* (1986)	0, 52 mg/m^3 6 h/d, 5 d/wk 72/sex MMAD, 1.7–2.5 µm; GSD, 1.9–2.1	Lung (epidermoid carcinomas): M–0/42 (control), 1/47 F–0/47 (control), 10/53	[NS] [$P < 0.002$]	
Rat, F344 (F) Lifespan Holland *et al.* (1983, 1986); Johnson *et al.* (1987)	0, 12 mg/m^3 6 h/d, 5 d/wk for 83 wk 62 animals MMAD, 2.24 µm; GSD, 1.75	Lung (tumours): 0/54 (control), 18/60 (11 adenocarcinomas, 3 squamous cell carcinomas, 6 adenomas)	[$P < 0.001$]	Nose-only inhalation exposure. Age unspecified
Rat, SPF F344 (M, F) 30 mo Muhle *et al.* (1989, 1991, 1995)	0, 1 mg/m^3 6 h/d, 5 d/wk for 24 mo 50/sex MMAD, 1.3 µm; GSD, 1.8	Lung (tumours): 3/100 (control M, F), 7/50 (M), 12/50 (F) M–1 adenoma, 3 adenocarcinomas, 2 benign cystic keratinizing squamous cell tumours, 1 adenosquamous carcinoma, 1 squamous cell carcinoma F–2 adenomas, 8 adenocarcinomas, 2 benign cystic keratinizing squamous cell tumours	Unspecified (M) [$P < 0.05$] (F)	
Rat, Wistar (F) Up to 35 mo Spiethoff *et al.* (1992)	0, 6.1, 30.6 mg/m^3 6 h/d, 5 d/wk for 29 d 90 animals MMAD, 1.8 µm; GSD, 2.0	0/85 (control), 37/82 (low dose), 43/82 (high dose) Multiple tumours/rat: 21 bronchiolo-alveolar adenomas, 43 bronchiolo-alveolar carcinomas, 67 squamous cell carcinomas, 1 anaplastic carcinoma	[$P < 0.0001$] (both doses)	Nose-only inhalation exposure

d, day or days; F, female; GSD, geometric standard deviation; h, hour or hours; M, male; MMAD, mass median aerodynamic diameter; mo, month or months; NS, not significant; wk, week or weeks

3.2 Intranasal administration

3.2.1 Mouse

Two groups of 40 female (C57xBALB/c) F_1 mice received a single intranasal instillation of 4 mg of synthetic *d*- or *l*-quartz. A group of 60 females received an intranasal instillation of saline. Survivors were killed at 18 months after treatment, and the incidence of lymphomas and leukaemias combined was 0/60 (controls), 2/40 (*d*-quartz), and 6/40 (*l*-quartz) (Ebbesen, 1991). [The Working Group noted that the study was not designed to detect silica-induced lung tumours, and also noted the lack of information on quartz retention.]

3.3 Intratracheal administration

See Table 3.2.

3.3.1 Mouse

A group of 30 male A/J mice, 11–13 weeks old, received weekly intratracheal instillations of 2.9 mg quartz for 15 weeks. A group of 20 mice received instillations of vehicle [unspecified]. Animals were killed 20 weeks after the instillations. The incidences of lung adenomas were 9/29 in the controls, and 4/20 for the silica-instilled mice, values that were not statistically different (McNeill *et al.*, 1990).

Ishihara *et al.* (2002) administered a single dose (2 mg in saline/mouse) of crystalline silica to a group of four C57BL/6N mice by intratracheal instillation to study subsequent genotoxic effects. A control group of four animals was instilled saline only. Silicotic lesions were observed in the lungs of the exposed mice, but no pulmonary neoplasms were observed after 15 months.

3.3.2 Rat

A group of 40 Sprague Dawley rats [sex unspecified] received weekly instillations of 7 mg quartz (Min-U-Sil) in saline for 10 weeks. Another groups of 40 rats received instillations of saline alone, and 20 rats remained untreated. Animals were observed over their lifespan. The incidence of lung tumours in quartz-treated rats was 6/36, 0/40 in the saline controls, and 0/18 in the untreated rats (Holland *et al.*, 1983).

Groups of 85 male F344 rats received a single intratracheal instillation of 20 mg quartz in deionized water, Min-U-Sil or novaculite, into the left lung. Controls were instilled with vehicle only. Interim sacrifices of ten rats were made at 6, 12, and 18 months with a final sacrifice at 22 months. The incidence of lung tumours in the Min-U-Sil-instilled rats was 30/67, in the novaculite-treated rats 21/72, and in controls 1/75. All of the lung tumours were adenocarcinomas, except for one epidermoid carcinoma in the novaculite-treated rats (Groth *et al.*, 1986).

Groups of male and female F344/NCr rats [initial number unspecified] received one intratracheal instillation of 12 or 20 mg quartz in saline or 20 mg of ferric oxide (non-fibrogenic dust) in saline. Interim sacrifices were made at 11 and 17 months with a final sacrifice at 26 months. There was a group of untreated controls observed at unscheduled deaths after 17 months. No lung tumours were observed in the ferric-oxide-treated rats and only one adenoma was observed in the untreated controls. The high incidences of benign and mainly malignant lung tumours observed in the quartz-treated rats is summarized in Table 3.3 (Saffiotti, 1990, 1992; Saffiotti *et al.*, 1996).

Six groups of 37–50 female Wistar rats, 15 weeks old, received either a single or 15 weekly intratracheal instillation of one of three types of quartz preparations in saline (see Table 3.4). A control group received 15 weekly instillations of saline. To retard the development of silicosis,

Table 3.2 Studies of cancer in experimental animals exposed to silica (intratracheal instillation)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start Particle size	Incidence of tumours	Significance
Mouse, A/J (M) 20 wk McNeill *et al.* (1990)	0, 2.9 mg Weekly for 15 wk 30, 20 (controls) 1–5 µm (size not further specified)	Lung (adenomas): 9/29 (control), 4/20 Tumour multiplicity: 0.31 ± 0.09 (control), 0.20 ± 0.09	[NS] [NS]
Rat, Sprague Dawley (NR) Lifespan Holland *et al.* (1983)	0 (saline), 7 mg Weekly for 10 wk 40 animals 1.71 ± 1.86 µm	Lung (1 adenoma, 5 carcinomas): 0/40 (control), 6/36	[*P*<0.05] (carcinomas)
Rat, F344 (M) 22 mo Groth *et al.* (1986)	0, 20 mg once only 85 animals < 5 µm	Lung (adenocarcinomas): 1/75 (control), 30/67	[*P*<0.001]
Rat, F344/NCr (M, F) 11, 17 or 26 mo Saffiotti (1990, 1992); Saffiotti *et al.* (1996)	0, 12, 20 mg quartz Once only Ferric oxide (20 mg) was negative control [Initial number of rats, NR] 0.5–2.0 µm	High incidences of benign and mainly malignant lung tumours in quartz-treated rats reported in Table 3.3 No tumours observed in ferric oxide group One adenoma in untreated controls	NR
Rat, Wistar Lifespan Pott *et al.* (1994)	0 (saline), one single or 15 weekly injections of one of 3 types of quartz Some rats received PVNO to protect against silicosis 37–50/group	Incidences of benign and malignant lung tumours in quartz-treated rats are shown in Table 3.4 No tumours observed in saline-treated rats	NR
Hamster Syrian Golden (NR) Lifespan Holland *et al.* (1983)	0 (saline), 3, 7 mg quartz (Min-U-Sil) Once a wk for 10 wk 48/group; 68 (controls) 1.71 ± 1.86 µm	No lung tumours in any group	
Hamster, Syrian Golden (M) Lifespan Renne *et al.* (1985)	0 (saline), 0.03, 0.33, 3.3, or 6.0 mg quartz (Min-U-Sil) weekly for 15 wk 25–27/group MMAD, 5.1 µm Geometric diameter, 1.0 µm	No lung tumours in any group	
Hamster, Syrian Golden (M) 92 wk Niemeier *et al.* (1986)	0 (saline), 1.1 (Sil-Co-Sil) or 0.7 (Min-U-Sil) mg One group received 3 mg ferric oxide 50/group 5 µm (Min-U-Sil)	No tumours in saline controls or in Sil-Co-Sil groups 1 adenosquamous carcinoma of the bronchi and lung in Min-U-Sil group and 1 benign tumour of the larynx in ferric oxide group	

M, male; MMAD, mass median aerodynamic diameter; mo, month or months; NR, not reported; NS, not significant; PVNO, polyvinylpyridine-*N*-oxide; wk, week or weeks

Table 3.3 Incidence, numbers, and histological types of lung tumours in F344/NCr rats after a single intratracheal instillation of quartz

Treatment		Observation time	Lung tumours	
Material	Dose[a]		Incidence	Types
Males				
Untreated	None	17–26 mo	0/32	
Ferric oxide	20 mg	11–26 mo	0/15	
Quartz (Min-U-Sil 5)	12 mg	Killed at 11 mo	3/18 (17%)	6 adenomas, 25 adenocarcinomas, 1 undifferentiated carcinoma, 2 mixed carcinomas, 3 epidermoid carcinomas
		Killed at 17 mo	6/19 (32%)	
		17–26 mo	12/14 (86%)	
Quartz (HF-etched Min-U-Sil 5)	12 mg	Killed at 11 mo	2/18 (11%)	5 adenomas, 14 adenocarcinomas, 1 mixed carcinoma
		Killed at 17 mo	7/19 (37%)	
		17–26 mo	7/9 (78%)	
Females				
Untreated	None	17–26 mo	1/20 (5%)	1 adenoma
Ferric oxide	20 mg	11–26 mo	0/18	
Quartz (Min-U-Sil 5)	12 mg	Killed at 11 mo	8/19 (42%)	2 adenomas, 46 adenocarcinomas, 3 undifferentiated carcinomas, 5 mixed carcinomas, 3 epidermoid carcinomas
		Killed at 17 mo	10/17 (59%)	
		17–26 mo	8/9 (89%)	
	20 mg	17–26 mo	6/8 (75%)	1 adenoma, 10 adenocarcinomas, 1 mixed carcinoma, 1 epidermoid carcinoma
Quartz (HF-etched Min-U-Sil 5)	12 mg	Killed at 11 mo	7/18 (39%)	1 adenoma, 36 adenocarcinomas, 3 mixed carcinomas, 5 epidermoid carcinomas
		Killed at 17 mo	13/16 (81%)	
		17–26 mo	8/8 (100%)	

[a] Suspended in 0.3 or 0.5 mL saline
HF, hydrogen fluoride; mo, month or months
From Saffiotti (1990, 1992), Saffiotti *et al.* (1996)

Table 3.4 Incidence, numbers, and histological types of lung tumours in female Wistar rats after intratracheal instillation of quartz

Material	Surface area	No. of instillations	No. of rats examined	No. and #% of rats with primary epithelial lung tumours[a]					Other tumours[b]
	(m^2/g)	(del # × mg)		Adenoma	Adenocarcinoma	Benign CKSCT	Squamous cell carcinoma	Total (%)	
Quartz (DQ 12)	9.4	15 × 3	37	0	1z	11	1 + 1y	38	1
Quartz (DQ 12) + PVNO	9.4	15 × 3	38	0	1 + 3z	8 + 1x	4+1x+3y+1z	58	2
Quartz (DQ 12)	9.4	1 × 45	40	0	1	7	1	23	2
Quartz (Min-U-Sil)	–	15 × 3	39	1	4 + 4z	6	1+2y+2z+1y,z	54	3
Quartz (Min-U-Sil) + PVNO	–	15 × 3	35	1	2 + 1x	8	5+1x+1y+1z	57	3
Quartz Sykron (F 600)	3.7	15 × 3	40	0	3	5	3 + 1z	30	1
0.9% Sodium chloride	–	15 × 0.4 mL	39	0	0	0	0	0	5

[a] If an animal was found to bear more than one primary epithelial lung tumour type, this was indicated as follows:[x]adenoma; [y]adenocarcinoma; [z]benign CKSCT.

[b] Other types of tumours in the lung: fibrosarcoma, lymphosarcoma, mesothelioma or lung metastases from tumours at other sites

PVNO, polyvinylpyridine-*N*-oxide; CKSCT, cystic keratinizing squamous cell tumour

From Pott *et al*. (1994)

two of the groups received injections of polyvinylpyridine-*N*-oxide. All groups of quartz-exposed rats had a significant increase in lung tumours, and the rats protected against silicosis developed more pulmonary squamous cell carcinomas than rats that were not protected (Pott *et al.*, 1994).

3.3.3 Hamster

Two groups of 48 Syrian hamsters [sex unspecified] received intratracheal instillations of 3 or 7 mg quartz (Min-U-Sil) in saline once a week for 10 weeks. A group of 68 hamsters received saline alone, and another group of 72 hamsters were untreated. All animals were observed for their lifespan. No lung tumours were observed in any of the groups (Holland *et al.*, 1983).

Groups of 25–27 male Syrian golden hamsters, 11–weeks old, received weekly intratracheal instillation of 0.03, 0.33, 3.3, or 6.0 mg quartz (Min-U-Sil) in saline for 15 weeks. Groups of 27 saline-instilled hamsters and 25 untreated controls were used as controls. Animals were observed for their lifespan. No lung tumours were observed in any group (Renne *et al.*, 1985).

Three groups of 50 male Syrian golden hamsters received weekly instillations of 1.1 mg of quartz as Sil-Co-Sil, or 0.7 mg of quartz as Min-U-Sil, or 3 mg of ferric oxide (non-fibrogenic particle) in saline for 15 weeks. A group of 50 saline-instilled hamsters served as controls. Survivors were killed at 92 weeks after the beginning of the instillations. No respiratory tract tumours were observed in the hamsters exposed to Sil-Co-Sil or in the saline controls. One adenosquamous carcinoma of the bronchi and lung was observed in the Min-U-Sil group, and one benign tumour of the larynx in the ferric-oxide-exposed group (Niemeier *et al.*, 1986).

3.4 Intrapleural and intrathoracic administration

3.4.1 Mouse

One mouse study was reported in the previous *IARC Monograph* (IARC, 1997) in which the route of exposure was via a single intrathoracic injection of tridymite. The study was only reported as an abstract, and therefore is not described here (Bryson *et al.*, 1974).

3.4.2 Rat

Two groups of 48 male and 48 female standard Wistar rats and two groups 48 male and 48 female SPF Wistar rats were given a single intrapleural injection of 20 mg alkaline-washed quartz (size, < 5 μm) in saline, and observed for their lifespan. Control rats received injections of 0.4 mL saline alone. Malignant tumours of the reticuloendothelial system involving the thoracic region were observed in 39/95 quartz-treated SPF rats [$P < 0.001$] (23 histiocytic lymphomas, five Letterer-Siwe/Hand-Schüller-Christian disease-like tumours, one lymphocytic lymphoma, four lymphoblastic lymphosarcomas, and six spindle cell sarcomas), and in 31/94 quartz-treated standard rats [$P < 0.001$] (30 histiocytic lymphomas and one spindle-cell sarcoma). In the SPF control animals, 8/96 rats had tumours (three lymphoblastic lymphosarcomas, five reticulum cell sarcomas), 7/85 standard rat controls had tumours (one lymphoblastic lymphosarcoma, and six reticulum cell sarcomas) (Wagner & Berry, 1969; Wagner, 1970; Wagner & Wagner, 1972). [The Working Group noted that the distribution of tumours over sexes was unspecified.]

In a second study, with the same dosing regimen and type of quartz, 23 rats developed malignant reticuloendothelial system tumours (21 malignant lymphomas of the histiocytic type [MLHT], two thymonas, and one lymphosarcoma/thymoma/spindle cell sarcoma) in 80 male

and 80 female SPF Wistar rats after 120 weeks. In another experiment, 16 male and 16 female SPF Wistar rats dosed similarly with Min-U-Sil quartz were observed until they were moribund. Eight of the 32 rats developed MLHT and three developed thymomas/lymphosarcomas. In a last experiment with the same experimental design, 18 of 32 SPF Wistar rats that had been injected with cristobalite developed malignant lymphomas (13 MLHT and five thymomas/lymphosarcomas). No MLHT and one thymoma/lymphosarcoma tumours were observed in 15 saline-injected control rats. (Wagner, 1976). [The Working Group noted that the distribution of tumours over sexes was unspecified, and that no statistics were provided.]

In one experiment, groups of 16 male and 16 female Wistar rats were given intrapleural injections of 20 mg of four types of quartz (Min-U-Sil, D&D, Snowit, and DQ12). The animals were observed for their lifespan. For all but the group treated with DQ12 quartz, there was a statistically significant increase in MLHT over saline controls (Table 3.5). In a second experiment with the same experimental design, two other strains of rats were injected Min-U-Sil (12 male and 12 female PVG rats and 20 male and 20 female Agus rats). A non-significant increase in MLHT was observed in both strains, and there was no MLHT in the saline controls. In a third experiment with the same experimental design, cristobalite was injected, and 4/32 treated Wistar rats developed MLHT [not significant], but none of the 32 saline controls did. In a final experiment, 16 male and 16 female Wistar rats were injected triolymite (size, < 0.5 µm; 0.35×10^6 particle/µg), and observed for their lifespan. A total of 16/32 Wistar rats developed MLHT, whereas no such tumours were observed in the 32 saline controls (Wagner *et al.*, 1980). [The Working Group noted that the distribution of tumours over sexes was unspecified.]

Two groups of 36 2-month-old male Sprague-Dawley rats, received a single intrapleural injection of 20 mg DQ12 quartz in saline or saline alone, and were observed for their lifespan. Twenty-seven male rats served as untreated controls. Six malignant histiocytic lymphomas and two malignant Schwannomas were observed in the quartz-treated group [not significant], and one chronic lymphoid leukaemia and one fibrosarcoma were observed in the saline group and untreated controls, respectively (Jaurand *et al.*, 1987).

3.5 Intraperitoneal administration

3.5.1 Rat

Two groups of 16 male and 16 female SPF Wistar rats received a single intraperitoneal injection of 20 mg of Min-U-Sil quartz in saline, and were observed for their lifespan. There were 12 saline controls [sex unspecified]. A total of 9/64 quartz-exposed rats developed malignant lymphomas (two MLHT and seven thymoma/lymphosarcomas). None of the saline controls developed MLHT, but one thymoma/lymphosarcoma was noted (Wagner, 1976). [The Working Group noted that the distribution of tumours over sexes was unspecified.]

3.6 Subcutaneous administration

3.6.1 Mouse

Two groups of 40 female (C57xBALB/c) F_1 mice received a single subcutaneous injection of 4 mg of *d*- or *l*-quartz. A group of 60 female mice served as saline controls. At 18 months after injection, there was an incidence of lymphomas/leukemias of 0/60, 1/40 and 12/40 ($P < 0.001$), and of liver adenomas of 0/60, 1/40 and 3/40 for the saline controls, *d*-quartz and *l*-quartz groups, respectively. No injection-site tumours were reported (Ebbesen, 1991).

Table 3.5 Incidences of malignant lymphoma of the histiocytic type (MLHT) in Wistar rats after an intrapleural injection of 20 mg quartz/animal

Sample	No. of particles × 10^6/µg	Size distribution (%)			Mean survival (days)	Incidence of MLHT (%)[a]
		< 1 µm	1–2 µm	2–4.6 µm		
Min-U-Sil (a commercially prepared crystalline quartz probably 93% pure)	0.59	61.4	27.9	9.1	545	11/32 (34%)b
D&D (obtained from Dowson & Dobson, Johannesburg, pure crystalline quartz)	0.30	48.4	33.2	18.4	633	8/32 (25%)b
Snowit (commercially prepared washed crystals)	1.1	81.2	12.9	5.6	653	8/32 (25%)b
DQ12 (standard pure quartz)	5.0	91.4	7.8	0.8	633	5/32 (16%)
Saline controls	–	–	–	–	717	0 [0/32] (0%)

[a] Sex unspecified
[b] [Significantly different from controls by Fisher Exact test, $P < 0.05$]
From Wagner *et al.* (1980)

3.7 Intravenous administration

3.7.1 Mouse

Groups of 25 male and 25 female strain A mice were injected in the tail vein with 1 mg quartz in 0.1 mL of saline, with a control group of 75 male and female untreated animals. Animals were killed 3, 4.5 or 6 months after injection. There was no difference in the incidences and multiplicities of pulmonary adenomas between treated and untreated animals (Shimkin & Leiter, 1940).

3.8 Administration with known carcinogens

3.8.1 Inhalation

(a) Rat

Studies have been completed to determine the effect of co-exposure to silica and Thorotrast, a known carcinogen (See Table 3.6). Two sets of three groups of 90 female Wistar rats, 6–8 weeks old, were exposed by inhalation to 0, 6, or 31 mg/m^3 of DQ12 quartz (mass median diameter, 1.8 µm; GSD, 2.0) for 6 hours/day 5 days/week for 29 days. One week after the inhalation exposure, one group of quartz-exposed rats and one group of sham-exposed rats received an intravenous injection of Thorotrast (2960 Bq ^{228}Th/mL, 0.6 mL). Controls were only sham-exposed. In each of the six groups, interim sacrifices of three or six animals each were made 0, 6, 12 and 24 months after the end of exposure. The experiment was terminated 34 months after the end of exposure. In rats that were exposed to silica by inhalation and then given Thorotrast, there was a small increase in lung tumours compared to the already high incidence of benign and malignant tumours induced by silica alone (Spiethoff *et al.*, 1992).

3.8.2 Intratracheal administration

(a) Rat

Four groups of white rats (group sizes varied from 28 to 70, with approximately equal numbers of males and females) were given either no treatment or a single instillation of 5 mg benzo[*a*]pyrene or an instillation of 50 mg quartz (size, 82% < 2 µm) and 5 mg benzo[*a*]pyrene (Group A) or 50 mg quartz and a later (1 month) instillation of 5 mg benzo[*a*]pyrene (Group B). The rats were observed until death. There were no

Table 3.6 Incidence, numbers and histological types of lung tumours in female Wistar rats after inhalation exposure to quartz and/or Thorotrast

Treatment	Number of rats[a]	Lung tumours				
		Incidence	Total number	Histological type		
		Observed		Bronchiolo-alveolar adenoma	Bronchiolo-alveolar carcinoma	Squarnuous cell carcinoma
Controls	85	–	–	–	–	–
Low-dose quartz	82	37	62	8	17	37
High-dose quartz	82	43	69	13	26	30
Thorotrast (Tho)	87	3	6	–	5	1
Low-dose quartz + Tho	87	39	68	10	28	30
High-dose quartz + Tho	87	57	98	16	47	35

[a] Without the animals sacrificed 0 and 6 months after the end of inhalation exposure.
From Spiethoff *et al.* (1992)

lung tumours in the untreated rats (0/45), nor in those exposed to benzo[*a*]pyrene alone (0/19). In the combined exposures to benzo[*a*]pyrene and quartz, an increased incidence in lung tumours was observed (Group A, 14/31, 11 squamous cell carcinomas and three papillomas; Group B, 4/18, two papillomas and two carcinomas) (Pylev, 1980). [The Working Group noted the absence of a group exposed to quartz alone.]

(b) Hamster

Groups of 50 male Syrian golden hamsters received weekly intratracheal instillations for 15 weeks in saline of 3 mg benzo[*a*]pyrene or 3 mg ferric oxide or 3 mg ferric oxide plus 3 mg benzo[*a*]pyrene or 1.1 mg Sil-Co-Sil or 1.1 mg Sil-Co-Sil plus 3 mg benzo[*a*]pyrene or 0.7 mg Min-U-Sil or 0.7 mg Min-U-Sil plus 3 mg benzo[*a*]pyrene or 7 mg Min-U-Sil or 7 mg Min-U-Sil plus 3 mg benzo[*a*]pyrene. Fifty male controls received saline alone. Survivors were killed at 92 weeks after exposure. Co-exposures with silica caused an enhancement of the number of respiratory tract tumours induced by benzo[*a*]pyrene (mainly in the bronchus and lung) (Niemeier *et al.*, 1986; Table 3.7).

3.9 Synthesis

Studies of the carcinogenicity of crystalline silica in experimental animal models have shown quartz dust to be a lung carcinogen in rats following inhalation and intratracheal instillation, but not in mice or hamsters. Rats are known to be more sensitive than are mice or hamsters to the induction of lung tumours due to other inhaled poorly soluble particles, such as carbon black (Mauderly *et al.*, 1994).

Quartz-induced lymphoma incidence was also increased in several experiments in rats after intrapleural administration, and in one study in mice after subcutaneous administration. Tridymite- and cristobalite-induced lymphomas were observed in only a single experiment.

Table 3.7 Incidences of respiratory tract tumours in Syrian golden hamsters after intratracheal administration of quartz with or without benzo[*a*]pyrene

Treatment	No. of animals	No. of animals with respiratory tract tumours	No. of respiratory tract tumours[a] by site			Mean latency (wk)
			Larynx	Trachea	Bronchus and lung	
Saline control	48	0	0	0	0	–
BaP	47	22	5	3	32	72.6
Ferric oxide	50	1	1	0	0	62
Ferric oxide + BaP	48	35b,c	5	6	69	70.2
Sil-Co-Sil	50	0	0	0	0	–
Sil-Co-Sil + BaP	50	36b,c	13	13	72	66.5
Min-U-Sil	50	1	0	0	1	68
Min-U-Sil + BaP	50	44b,c	10	2	111	68.5
Min-U-Sil + ferric oxide	49	0	0	0	0	–
Min-U-Sil + ferric oxide + BaP	50	38b,c	10	4	81	66.7

[a] Types of tumours: polyps, adenomas, carcinomas, squamous cell carcinomas, adenosquamous carcinomas, adenocarcinomas, sarcomas.
[b] Statistically significantly higher ($P < 0.00001$; two-tailed Fisher Exact test) compared with the corresponding group not treated with BaP.
[c] Statistically significantly higher ($P < 0.01$; two-tailed Fisher Exact test) compared with the BaP group.
BaP, benzo[*a*]pyrene
From Niemeier *et al.* (1986)

4. Other Relevant Data

4.1 Deposition and biopersistence

The inhalation of crystalline silica is associated with various lung diseases including acute silicosis or lipoproteinosis, chronic nodular silicosis, and lung cancer. Exposure to silica dust may also cause renal and autoimmune diseases (Steenland & Goldsmith, 1995; Stratta *et al.*, 2001; Cooper *et al.*, 2002; Otsuki *et al.*, 2007). In silicotic patients, alveolar macrophages collected by pulmonary lavage contain crystalline silica and at autopsy, elevated levels of quartz are found in the lungs and lymph nodes. Crystalline silica is poorly soluble and biopersistent; even after cessation of exposure, silicosis can progress and is a risk factor for the development of lung cancer (IARC, 1997).

Alveolar macrophages play a key role in silica-related toxicity, and therefore the cytotoxic potency of silica particles determine the degree of silica-related pathogenicity (IARC, 1997; Donaldson & Borm, 1998). The stronger the cytotoxicity of crystalline silica to alveolar macrophages, the higher the intensity of the inflammatory reaction, and the longer the residence time of the particle in the lung (Donaldson & Borm, 1998; Fenoglio *et al.*, 2000a).

Rodent inhalation studies have investigated the relationship between intrinsic particle toxicity, persistent inflammation, altered macrophage-mediated clearance, and biopersistence in the lung (Warheit *et al.*, 2007). Crystalline silica particles induce lung inflammation that persists even after cessation of exposure, with alveolar macrophages having reduced chemotactic responses and phagocytosis. Crystalline silica impairs macrophage-mediated clearance secondary to its cytotoxicity that allows these particles to accumulate and persist in the lungs (IARC, 1997). In humans, it is possible that co-exposure to tobacco smoke and crystalline silica may impair the clearance of these toxic particles (IARC, 2004).

4.2 Mechanisms of carcinogenicity

It is generally accepted that alveolar macrophages and neutrophils play a central role in diseases associated with exposure to crystalline silica (Hamilton *et al.*, 2008). An inflammation-based mechanism as described in IARC (1997) is a likely mechanism responsible for the induction of lung cancer associated with exposure to crystalline silica, although reactive oxygen species can be directly generated by crystalline silica polymorphs themselves, and can be taken up by epithelial cells. For this reason, a direct effect on lung epithelial cells cannot be excluded (Schins, 2002; Fubini & Hubbard, 2003; Knaapen *et al.* 2004).

4.2.1 *Physicochemical features of crystalline silica dusts associated with carcinogenicity*

The major forms or polymorphs of crystalline silica are the natural minerals quartz, tridymite, cristobalite, coesite, stishovite, and the artifical silica-based zeolites (porosils) (Fenoglio *et al.*, 2000a). Humans have been exposed only to quartz, tridymite, cristobalite, the other forms being very rare. Several amorphous forms of silica exist, some of which were classified in Group 3 (*not classifiable as to their carcinogenicity*) in the previous *IARC Monograph* (IARC, 1997). Also, it has been shown that this cytotoxicity is lowered with lowering hydrophilicity (Fubini *et al.*, 1999), which depends upon the circumstances under which the surface was created. For example, silica in fly ashes or volcanic dusts is generated at high temperatures, and is mostly hydrophobic.

The classification in Group 1 (*carcinogenic to humans*) of some silica polymorphs in the previous *IARC Monograph* (IARC, 1997) was preceded by a preamble indicating that crystalline silica did not show the same carcinogenic potency in all circumstances. Physicochemical features – polymorph characteristics, associated contaminants – may account for the differences found in humans and in experimental studies. Several studies on a large variety of silica samples, aiming to clarify the so-called “variability of quartz hazard” have indicated features and contaminants that modulate the biological responses to silica as well as several surface characteristics that contribute to the carcinogenicity of a crystalline silica particle (Donaldson & Borm, 1998; Fubini, 1998a; Elias *et al.*, 2000; Donaldson *et al.*, 2001). The larger potency of freshly ground dusts (e.g. as in sandblasting) has been confirmed in several studies; Vallyathan *et al.*, 1995), as immediately after cleavage, a large number of surface-active radicals are formed that rapidly decay (Damm & Peukert, 2009). The association with clay or other aluminium-containing compounds inhibits most adverse effects (Duffin *et al.*, 2001; Schins *et al.*, 2002a), iron in traces may enhance the effects but an iron coverage inhibits cytotoxicity and cell transformation (Fubini *et al.*, 2001). One study on a large variety of commercial quartz dusts has shown a spectrum of variability in oxidative stress and inflammogenicity *in vitro* and *in vivo*, which exceeds the differences previously found among different polymorphs (Bruch *et al.*, 2004; Cakmak *et al.*, 2004; Fubini *et al.*, 2004; Seiler *et al.*, 2004). Subtle differences in the level of contaminants appear to determine such variability. New studies *in vitro* and *in vivo* on synthesized nanoparticles of quartz (Warheit *et al.*, 2007) indicate a variability of effects also at the nanoscale. These new data clearly show that more or less pathogenic materials are comprised under the term “crystalline silica dusts.” However, most studies, so far, have failed to identify strict criteria to distinguish between potentially more or less hazardous forms of crystalline silica.

The pathogenic potential of quartz seems to be related to its surface properties, and the surface properties may vary depending on the origin of the quartz. The large variability in silica hazard even within quartz particles of the same polymorph may originate from the

grinding procedure, the particle shape, the thermal treatment (determines the hydrophilicity of the particle), and the metal impurities (e.g. aluminium, iron) (Fubini *et al.*, 2004).

The toxicity of silica dust from various sources may be related either to the kind of silica polymorph or to impurities.

The correlation between artificially pure crystalline silicas (porosils) with similar physicochemical properties, but different micromorphology, size and surface area, was investigated (Fenoglio *et al.*, 2000a). Surface area and aspect ratio (elongated crystals with a higher aspect ratio than more isometric crystals) of the particulates tested in a cellular system (mouse monocyte-macrophage tumour cell line) correlate best with inhibition of cell proliferation after 24–72 hours experimental time. From the natural crystalline silicas, only stishovite did not show a cytotoxic effect; all the other natural polymorphs were rather toxic. Stishovite is made up of smooth round particles (Cerrato *et al.*, 1995) whereas quartz, tridymite, and cristobalite consist of particles with very sharp edges caused by grinding (Fubini, 1998a; Fubini *et al.*, 1990, 1999). Stishovite, the only polymorph with silicon in octahedral coordination, has densely packed hydroxyl-silanols on its surface that interact with hydrogen bonds with each other; for this reason, the interaction of silanols with cell membranes, which normally does occur, is dramatically reduced (Cerrato *et al.*, 1995).

Pure silica-zeolites with different particle forms exhibit similar cytotoxicity *in vitro* if compared at equal surface area instead of equal mass. The extent of free radical generation did not show a significant correlation with cytotoxicity in this short-term in-vitro test (Fenoglio *et al.*, 2000a). Free radicals generated by the particle may play a role in later stages of toxicity related to crystalline silica (Ziemann *et al.*, 2009). Both silicon-based surface radicals and iron ions located at the particle surface may be active centres for free radical release in solution (Fubini *et al.*, 2001).

As has already been demonstrated with quartz and cristobalite (Brown & Donaldson, 1996; Bégin *et al.*, 1987), the cytotoxicity of artificially pure silica-zeolites can be decreased by aluminium ions adsorbed onto the particle surface (Fenoglio *et al.*, 2000a). Crystalline silica may occur naturally embedded in clays or may be mixed with other materials in some commercial products. It is possible that these materials may adsorb onto the silica surface, and modify its reactivity. However, the extent of surface coverage and the potency of these modified crystalline silica particles after long-term residence in the lungs have not been systematically assessed.

A quartz sample isolated from bentonite clay obtained from a 100 to 112 million-year-old formation in Wyoming, USA, exhibits a low degree of internal crystal organization, and the surface of this quartz particles are occluded by coatings of the clay. This "quartz isolate" was compared in respect to its toxic potency after intratracheal instillation in rats with the quartz sample DQ12. The "quartz isolate" showed a much lower toxicity than DQ12 quartz, in agreement with the much lower surface reactivity of "quartz isolate" compared to the DQ12 quartz (Creutzenberg *et al.*, 2008; Miles *et al.*, 2008).

4.2.2 Direct genotoxicity and cell transformation

Reactive oxygen species are generated not only at the particle surface of crystalline silica, but also by phagocytic and epithelial cells exposed to quartz particles (Castranova *et al.*, 1991; Deshpande *et al.*, 2002). Oxidants generated by silica particles and by the respiratory burst of silica-activated phagocytic cells may cause cellular and lung injury, including DNA damage. Lung injury may be initiated and amplified by severe inflammation (Donaldson *et al.*, 2001; Castranova 2004; Knaapen *et al.*, 2004). Various

products (chemotactic factors, cytokines, growth factors) released by activated (and also dying) alveolar macrophages will not only recruit more macrophages as well as polymorphonuclear leukocytes (PMNs) and lymphocytes, but may also affect and activate bronchiolar and alveolar epithelial cells.

Reactive oxygen species can directly induce DNA damage (Knaapen *et al.*, 2002; Schins *et al.*, 2002b), and morphological transformations observed in Syrian hamster embryo (SHE) cells correlate well with the amount of hydroxyl radicals generated (Elias *et al.*, 2000, 2006; Fubini *et al.*, 2001). Neoplastic transformation was observed in in-vitro assays in the absence of secondary inflammatory cells (Hersterberg *et al.*, 1986; Saffiotti & Ahmed, 1995; Elias *et al.*, 2000). There seems to be no correlation between the extent of cytotoxicity as assessed by colony-forming efficiency and transforming potency (SHE test) when various quartz samples were investigated (Elias *et al.*, 2000). In contrast to transforming potency, which was clearly related to hydroxyl radical generation, cytotoxicity was not affected by antioxidants. Partial reduction of transforming potency when deferoxamine-treated quartz was used points to the role of transitional metals, e.g. iron on the particle surface in generating hydroxyl radicals (Fubini *et al.*, 2001). The SHE test used in this study by Fubini *et al.* (2001) and by others is recommended by the Centre for the Validation of Alternative Methods (ECVAM) as an alternative method for investigating the potential carcinogenicity of particulates (Fubini, 1998b). In nude mice injected with these transformed cells, tumours could be initiated (Saffiotti & Ahmed, 1995).

Particle uptake by target cells is also relevant for direct genotoxicity (Schins, 2002). Crystalline silica particles were detected in type II lung epithelial cells (RLE-6TN) *in vitro*; these particles were located also in close proximity to the nuclei and mitochondria, but not within these organelles. An osteosarcoma cell line lacking functional mitochondria was investigated with respect to quartz-related DNA damage with an osteosarcoma cell line with normal mitochondria. Only the cell line with functioning mitochondria showed significantly increased DNA damage after exposure to DQ12 quartz (Li *et al.*, 2007).

The relationship between genotoxic effects (formation of DNA strand breaks) and the uptake of quartz particles was investigated *in vitro* with A549 human lung epithelial cells (Schins *et al.*, 2002a). The percentage of A549 cells containing particles was clearly lower after exposure to quartz coated with polyvinylpynidine-*N*-oxide or aluminum lactate compared to uncoated quartz (DQ12). In this experiment, DNA strand breaks measured (Comet assay) in the exposed cells correlated very well with the number of particles absorbed by the cells. It could also be demonstrated that the generation of reactive oxygen species was closely related to the formation of DNA strand breaks (Schins, 2002). However, in other in-vitro studies using different quartz species, DNA strand breaks in epithelial cells could be observed only at particle concentrations that caused cytotoxicity (Cakmak *et al.*, 2004).

Rats were exposed to crystalline silica for 3 hours and sacrificed at different time points after exposure, and lungs were examined by electron microscopy. The lungs were fixed by vascular perfusion through the right ventricle. In these investigations, silica crystals were found within the cytoplasm of type I lung epithelial cells (Brody *et al.*, 1982). Although type I cells are not the target cell for tumour formation, these data show that the uptake of quartz particles in epithelial lung cells *in vivo* is in principle possible. Other particles including titanium dioxide, carbon black, or metallic particles have occasionally been found in type I lung epithelial cells in rats after inhalation exposure (Anttila, 1986; Anttila *et al.*, 1988; Nolte *et al.*, 1994).

After intratracheal instillation of DQ12 quartz, DNA strand breaks could be observed in lung epithelial cells isolated from quartz-treated rats. This effect was not found when the quartz dust was treated with either polyvinylpyridine-*N*-oxide or aluminium lactate. This finding suggests an important role of the reactive surface of quartz-induced DNA damage *in vivo*. No increase in alkaline phosphatase was found in the bronchiolo-alveolar lavage fluid of quartz-treated rats, and therefore, as alkaline phosphatase is an enzyme specifically present in type II epithelial cells, it can be assumed that there was no obvious cytotoxicity in these lung cells. These data support the current view of the important role of inflammatory cells in quartz-induced genotoxic effects (Knaapen *et al.*, 2002).

4.2.3 Depletion of antioxidant defences

Substantial amounts of ascorbic acid (Fenoglio *et al.*, 2000b) and glutathione (Fenoglio *et al.*, 2003) are consumed in the presence of quartz in cell-free tests via two different surface reactions. Both reactions may deplete antioxidant defences in the lung-lining fluid, thereby enhancing the extent of oxidative damage.

Incubation of murine alveolar MH-S macrophages with quartz particles (80 µg/cm^2) for 24 hours inhibited glucose 6-phosphate dehydrogenase (G6PD)-1 activity by 70%, and the pentose phosphate pathway by 30%. Such effects were accompanied by a 50% decrease in intracellular glutathione. Quartz inhibits G6PD but not other oxidoreductases, and this inhibition is prevented by glutathione, suggesting that silica contributes to oxidative stress also by inhibiting the pentose phosphate pathway, which is critical for the regeneration of reduced glutathione (Polimeni *et al.*, 2008).

4.2.4 Indirect mechanisms

After 13 weeks of inhalation exposure to 3 mg/m^3 crystalline silica (mass median aerodynamic diameter, 1.3 µm) or 50 mg/m^3 amorphous silica (mass median aerodynamic diameter, 0.81 µm), the percentage of PMNs in the lung of the exposed rats was similar after each exposure. However, HPRT mutation frequency of the alveolar epithelial cells was significantly increased only in rats exposed to crystalline silica. Other factors including toxic effects to epithelial cells, solubility, and biopersistence may also be important for the induction of these mutagenic effects (Johnston *et al.*, 2000). A specific finding in rats treated intratracheally with amorphous silica (Aerosil®150, pyrogenic silica with primary particle size of 14 nm) was a severe granulomatous alveolitis which over time progressed to “scar-like” interstitial fibrotic granulomas not seen after crystalline silica exposure in rats (Ernst *et al.*, 2002). Lung tumours were found in rats also after the repeated intratracheal instillation of the same amorphous silica (Kolling *et al.*, 2008).

Toxic mineral dusts, especially crystalline silica, have unique, potent effects on alveolar macrophages that have been postulated to trigger the chain of events leading to chronic lung fibrosis (silicosis) and lung cancer (Hamilton *et al.*, 2008). Macrophages express a variety of cell-surface receptors that bind to mineral dusts leading to phagocytosis, macrophage apoptosis, or macrophage activation. The major macrophage receptor that recognizes and binds inhaled particles as well as unopsonized bacteria is MARCO (Arredouani *et al.*, 2004, 2005). Additional members of the macrophage-scavenger receptor family responsible for binding mineral particles as well as a wide range of other ligands include SR-AI and SR-AII (Murphy *et al.*, 2005). Although SR-AI/II and MARCO bind both toxic and non-toxic particles, only crystalline silica triggers macrophage apoptosis following

binding to these scavenger receptors (Hamilton *et al.*, 2008). Other receptors expressed by macrophages and other target cells in the lung that bind mineral dusts include complement receptor and mannose receptors (Gordon, 2002). The pathological consequences of silica-induced injury to alveolar macrophages followed by apoptosis is impaired alveolar-macrophage-mediated clearance of crystalline silica as discussed in Section 4.1. Lysosomal membrane permeabilization following phagocytosis of crystalline silica particles has been hypothesized to enhance IL-1β secretion (Hornung *et al.*, 2008), and to trigger the release of cathepsin D, leading to mitochondrial damage, and the apoptosis of alveolar macrophages (Thibodeau *et al.*, 2004). Macrophage injury and apoptosis may be responsible for the increased susceptibility of workers exposed to silica to develop autoimmune disease (Pfau *et al.*, 2004; Brown *et al.*, 2005), and pulmonary tuberculosis (IARC, 1997; Huaux, 2007).

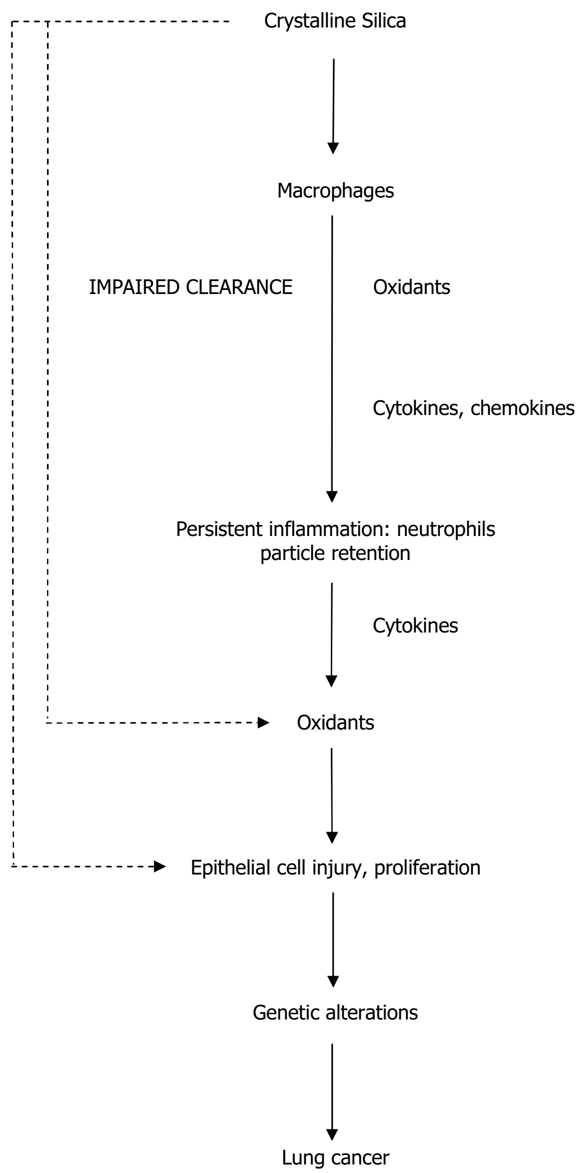
Persistent inflammation triggered by crystalline silica (quartz) has been linked to indirect genotoxicity in lung epithelial cells in rats, see Fig. 4.1 (IARC, 1997). Rats exposed to crystalline silica develop a severe, prolonged inflammatory response characterized by elevated neutrophils, epithelial cell proliferation, and development of lung tumours (Driscoll *et al.*, 1997). These persistent inflammatory and epithelial proliferative responses are less intense in mice and hamsters, and these species do not develop lung tumours following exposure to crystalline silica or other poorly soluble particles (IARC, 1997). There has been considerable discussion of whether the response of rats to inhaled particles is an appropriate model for the exposed response of humans (ILSI, 2000). Comparative histopathological studies of rats and humans exposed to the same particulate stimuli reveal more severe inflammation, alveolar lipoproteinosis, and alveolar epithelial hyperplasia in rats than in humans (Green *et al.*, 2007). These studies suggest that rats are more susceptible to develop persistent lung inflammation in response to particle inhalation than other species (ILSI, 2000).

Chronic exposure of rats to crystalline silica also leads to pulmonary fibrosis (Oberdörster, 1996), and workers with silicosis have an elevated risk of developing lung cancer (Pelucchi *et al.*, 2006). The causal association between chronic inflammation, fibrosis, and lung cancer was reviewed by IARC (2002). These associations provide a biological plausible mechanism between inflammation and the development of fibrosis and/or lung cancer (Balkwill & Mantovani, 2001).

4.3 Molecular pathogenesis of cancer of the lung

Acquired molecular alterations in oncogenes and tumour-suppressor genes characterize the multistage development of lung cancer (Sato *et al.*, 2007). Somatic alterations, such as DNA adducts, develop in the respiratory tract of smokers during the early stages of carcinogenesis (Wiencke *et al.*, 1999). Specific point mutations in in the *K-RAS* oncogene and the *p53* tumour-suppressor gene are considered as biomarkers of exposure to chemical carcinogens in tobacco smoke (Pfeifer *et al.*, 2002). Only one study has investigated the mutational spectrum of these genes that may be used as biomarkers for exposure to crystalline silica. Liu *et al.* (2000) analysed the mutation spectra in the *K-RAS* and *p53* genes in lung cancers that developed in workers with silicosis [smoking status unknown]. In a series of 36 cases, 16 mutations in exons 5, 7 and 8 of the *p53* gene were found. In contrast to non-occupational lung cancers, seven of these mutations clustered in exon 8. Most of the *K-RAS* gene mutations in non-small cell lung carcinomas occur at codon 12. Liu *et al.* (2000) did not detect this mutation in their case series of silicotics. Six mutations were found at codon 15 in exon 1 as well as additional mutations in codons 7, 15, 20, and

Fig. 4.1 Proposed mechanisms for the carcinogenicity of crystalline silica in rats



21. Most of these mutations were G→C transversions in contrast to G→T transversions at codon 12, which are characteristic of non-small cell lung cancers associated with tobacco smoking. If these specific mutations are confirmed in a larger series of lung cancers in silicotics, these could provide early biomarkers for the development of lung cancer in workers exposed to crystalline silica.

In a rat model of silica-induced lung cancer, a low frequency of *p53* gene mutations and no mutations in *K-RAS, N-RAS,* or *c-H-RAS* oncogenes were observed (Blanco *et al.*, 2007). No mutations in oncogenes or tumour-suppressor genes have been directly linked with exposure to crystalline silica.

The epigenetic silencing of the *p16^INK4a^* (Belinsky *et al.*, 2002), *CDH13,* and *APC* genes has also been found in a rat model of lung cancer induced by intratracheal instillation of crystalline silica (Blanco *et al.*, 2007). In this rodent model, the increased expression of iNOS

(inducible nitric oxide synthase) was also found in preneoplastic lesions, which is consistent with a role for reactive nitrogen species in silicosis (Porter *et al.*, 2006).

4.4 Species differences and susceptible populations

In rat chronic inhalation studies using crystalline silica or granular, poorly soluble particles, female rats are more susceptible than males to the induction of lung tumours. Overall, rats are susceptible to the induction of lung cancer following the exposure to crystalline silica or granular, poorly soluble particles, but hamsters and mice are more resistant. The mechanistic basis for these sex and species differences is unknown. Mice exposed to crystalline silica by intranasal instillation or subcutaneous injection, as well as rats injected intrapleurally or intraperitoneally develop lymphomas. Following inhalation exposure to crystalline silica, lymphomas have not been observed in any species (see Section 3).

In some workers exposed to crystalline silica, cytokine gene polymorphisms have been linked with silicosis (Yucesoy *et al.*, 2002). Specific polymorphisms in genes encoding in *TNF-α* and *IL-1RA* (interleukin-1 receptor antagonist) have been associated with an increased risk for the development of silicosis (Yucesoy & Luster, 2007). Gene–linkage analyses might reveal additional markers for susceptibility to the development of silicosis and lung cancer in workers exposed to crystalline silica.

4.5 Synthesis

Three mechanisms have been proposed for the carcinogenicity of crystalline silica in rats (Fig. 4.1). First, exposure to crystalline silica impairs alveolar-macrophage-mediated particle clearance thereby increasing persistence of silica in the lungs, which results in macrophage activation, and the sustained release of chemokines and cytokines. In rats, persistent inflammation is characterized by neutrophils that generate oxidants that induce genotoxicity, injury, and proliferation of lung epithelial cells leading to the development of lung cancer. Second, extracellular generation of free radicals by crystalline silica depletes antioxidants in the lung-lining fluid, and induces epithelial cell injury followed by epithelial cell proliferation. Third, crystalline silica particles are taken up by epithelial cells followed by intracellular generation of free radicals that directly induce genotoxicity.

The Working Group considers the first mechanism as the most prominent based on the current experimental data using inhalation or intratracheal instillation in rats, although the other mechanisms cannot be excluded. It is unknown which of these mechanisms occur in humans exposed to crystalline silica dust. The mechanism responsible for the induction of lymphomas in rats and mice following direct injections of crystalline silica dust is unknown.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of crystalline silica in the form of quartz or cristobalite. Crystalline silica in the form of quartz or cristobalite dust causes cancer of the lung.

There is *sufficient evidence* in experimental animals for the carcinogenicity of quartz dust.

There is *limited evidence* in experimental animals for the carcinogenicity of tridymite dust and cristobalite dust.

Crystalline silica in the form of quartz or cristobalite dust is *carcinogenic to humans (Group 1)*.

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WOOD DUST

Wood dust was considered by a previous IARC Working Group in 1994 (IARC, 1995), although wood-related occupations (i.e. Furniture and Cabinet-making) had been considered by IARC Working Groups earlier, in 1980 and 1987 (IARC, 1981, 1987). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification, chemical, and physical properties of the agent

Wood dust, generated in the processing of wood for a wide range of uses, is a complex substance. Its composition varies considerably according to the species of tree being processed. Wood dust is composed mainly of cellulose (approximately 40–50%), polyoses, lignin, and a large and variable number of substances of lower relative molecular mass which may significantly affect the properties of the wood. These include non-polar organic extractives (fatty acids, resin acids, waxes, alcohols, terpenes, sterols, steryl esters, and glycerides), polar organic extractives (tannins, flavonoids, quinones, and lignans) and water-soluble extractives (carbohydrates, alkaloids, proteins, and inorganic material) (IARC, 1995).

Trees are characterized botanically as gymnosperms (principally conifers, generally referred to as 'softwoods'), and angiosperms (principally deciduous trees, generally referred to as 'hardwoods'). Softwood and hardwood are not botanical concepts, referring to the species of tree and not directly describing the hardness of wood. Out of 12000 different species of trees, only about 800 are coniferous or softwoods, but roughly two-thirds of the wood used commercially worldwide belongs to the group of softwoods. Hardwoods tend to be somewhat more dense, and have a higher content of polar extractives than softwoods (IARC, 1995). For a comparison of softwoods and hardwoods, see Table 1.1.

For detailed descriptions of the classification and nomenclature, anatomical features, cell-wall structures, distribution of components of wood, and chemical components of wood, see the previous *IARC Monograph* (IARC, 1995), Nimz *et al.* (2005), and Kretschmann *et al.* (2007).

1.2 Occupational exposure

The wood species used in wood-related industries vary greatly by region and by type of product. Both hardwoods and softwoods (either domestically grown or imported) are used in the manufacture of furniture. Logging, sawmills, plywood, and particle-board manufacture generally involve the use of trees grown locally (IARC,

Table 1.1 Comparison of softwoods and hardwoods

Characteristic	Gymnosperms/conifers/softwoods	Angiosperms/deciduous wood/ hardwoods
Density (g/cm^3)	White (silver) fir: mean, 0.41 (0.32–0.71) European spruce: mean, 0.43 (0.30–0.64) Scots pine: mean, 0.49 (0.30–0.86)	European beech 0.68 (0.49–0.88) European oak 0.65 (0.39–0.93)
Fibres	Long (1.4–4.4 mm)	Short (0.2–2.4 mm)
Cell type	One (tracheids)	Various
Cellulose	~40–50%	~40–50%
Unit	β-D-Glucose	β-D-Glucose
Fibre pulp	Long	Short
Polyoses	~15–30%	~25–35%
Units	More mannose More galactose	More xylose
Lignin	~25–35%	~20–30%
Units	Mainly guaiacyl	Mainly syringyl or guaiacyl
Methoxy group content	~15%	~20%
Extractives content		
Non-polar (e.g. terpenes)	High	Low
Polar (e.g. tannins)	Low	High

Reprinted in part from Volume 62 (IARC, 1995)

1995). For detailed descriptions of historical exposures to wood dust and other agents in the workplace, see the previous *IARC Monograph* (IARC, 1995).

1.2.1 Extent of occupational exposure

Kauppinen *et al.* (2006) used nearly 36000 exposure measurements to estimate the occupational exposure to inhalable wood dust by country, industry, the level of exposure and type of wood dust in 25 Member States of the European Union. In 2000–03, approximately 3.6 million workers in the European Union [and undoubtedly millions more worldwide] were exposed occupationally to inhalable wood dust. The estimated number of workers exposed by industry and the number exposed to a level exceeding 5 mg/m^3 are shown in Table 1.2. The highest exposure levels were estimated to occur in the construction sector and furniture industry. Due to limited exposure data, there was considerable uncertainty in the estimates concerning construction woodworkers. About 560000 workers (16% of the number of workers exposed) may have been exposed to a level of inhalable wood dust that exceeded 5 mg/m^3. Mixed exposures to more than one species of wood and dust from wooden boards was very common, but reliable data on exposure to different species of wood could not be retrieved.

The US National Occupational Exposure Survey, carried out during 1981–83 in the United States of America, estimated that about 600000 workers were exposed to wood dust. The largest numbers of exposed workers were employed in the building trades (n = 134090), and the lumber/ wood product industries (n = 153543). Forestry workers (e.g. lumberjacks using chainsaws) were not considered to be exposed in this survey (NIOSH, 1990).

Table 1.2 WOODEX: Estimated number of workers exposed to wood dust in the 25 Member States of the European Union, 2000–03

Industry	Number employed	Number exposed	Exposed (% of employed)	Number exposed > 5 mg/m³
Construction	13 million	1.2 million	9	254000
Manufacture of furniture	1.2 million	713000	59	86500
Manufacture of joinery	472000	330000	71	42000
Forestry	445000	148000	33	< 100
Building of ships and boats	294000	31000	11	9600
Sawmilling	259000	196000	76	20000
Manufacture of other wood products	147000	97000	66	15500
Manufacture of wooden boards	124000	92000	74	8400
Manufacture of wooden containers	80000	57000	71	8600
All other employment	163 million	709000	0.4	118000
Total	179 million	3.6 million	2.0	563000

From Kauppinen *et al.* (2006)

1.2.2 Levels of occupational exposure

The highest exposures to wood dust have generally been reported in wood furniture and cabinet manufacture, especially during machine-sanding and similar operations (with wood dust levels frequently above 5 mg/m³). Exposure levels above 1 mg/m³ have also been measured in the finishing departments of plywood and particle-board mills, where wood is sawn and sanded, and in the workroom air of sawmills and planer mills near chippers, saws, and planers. Exposure to wood dust also occurs among workers in joinery shops, window and door manufacture, wooden boat manufacture, installation and refinishing of wood floors, pattern and model making, pulp and paper manufacture, construction carpentry, and logging. Measurements are generally available only since the 1970s, and exposures may have been higher in the past because of less efficient (or non-existent) local exhaust ventilation or other measures to control dust (IARC, 1995).

Woodworking machines have increased greatly in efficiency since the industrial revolution, and the increased speed of production has resulted in the generation of more dust. The increased efficiency may also result in exposure to finer wood dust particles than in the past, because smoother surfaces can be produced, and because saws and bits may retain their sharpness for longer. The introduction of engineering controls in some industries in some parts of the world, especially since the 1950s, has, however, reduced the exposure of workers considerably. Unfortunately, engineering controls, even if properly maintained, are not always effective, and the dust generated by hand-held power tools, particularly sanders, is much more difficult to control (IARC, 1995).

Studies published since the previous *IARC Monograph* reporting wood dust concentrations are presented in Table 1.3.

1.2.3 Particle size distribution

Chung *et al.* (2000) characterized the quantity, particle size distribution and morphology of dust created during the machining of medium-density fibreboard (MDF) in a controlled environment (a 2 × 2 × 2 m³ dust chamber). In terms of particle size distribution and morphology, the dust generated by machining MDF was generally found to be comparable with the dust generated by similarly machining hardwood or softwood. The quantity of dust generated during sanding

Table 1.3 Wood dust concentrations in various industries around the world

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of wood dust (mg/m³)	Number of samples	Comments
Sawmills and lumber mills				
Demers *et al.* (2000), Teschke *et al.* (1999b) Softwood lumber mill British Columbia, Canada July–August 1996	Sawmill, planer mill, and yard	*Geometric mean (GSD)* Inhalable particulate: 1.0 (2.7) Estimated wood dust: 0.5 (3.1)	220	Exposure assessment conducted for cross-sectional study of respiratory health among 275 softwood lumber mill workers; mill processed spruce (*Picea engelmannii* and *glauca*), pine (*Pinus contorta*), and fir (*Abies lasiocarpa*); random sampling strategy; full-shift (7–8 hours) personal inhalable particulate samples collected using seven-hole inhalable dust samplers; wood dust exposure estimated using the resin acid content within dust in combination with observations of job tasks, proximity to dust sources and use of personal protective equipment
Rosenberg *et al.* (2002) Sawmill, Finland 1997–99	Sawhouse - pine processing - spruce processing	*Range of geometric means* Inhalable particulate: 0.5–2.2 Inhalable particulate: 0.4–1.9	237 (178 personal)	Measured exposure of 22 sawhouse workers in mills processing pine (*Pinus silvestris*) and spruce (*Picea abies*); full-shift area and personal inhalable particulate samples collected in breathing zone; exposure measured during evening shift on three consecutive days; IOM samplers to collect inhalable dust; gravimetric determination of inhalable dust; assumption that all or most of inhalable dust originated from wood dust
Hall *et al.* (2002), Sawmills British Columbia, Canada 1981–97	Lumber mill	*Geometric mean (GSD)* 0.72 (3.49)	1237	Analysis of compliance data set (and a nested subset of research data) containing personal exposure measurements to wood dust at 77 lumber mills; 23% of database were research samples, 77% were compliance samples; an empirical “determinants of exposure” model created using multiple linear regression

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of wood dust (mg/m³)	Number of samples	Comments
Rusca *et al.* (2008), Sawmill Switzerland June–October 2002	Sawmill	*Mean (range)* Inhalable particulate: 1.7 (0.2–8.5)	NR	Cross-sectional survey of male employees at 12 sawmills processing spruce and fir species in the French part of Switzerland; personal measurements of inhalable dust collected using IOM samplers; gravimetric analysis of inhalable dust
Miscellaneous wood-related occupations				
Edman *et al.* (2003) Wood pellets and briquettes Sweden	Industrial production of wood pellets and briquettes	*Geometric mean (range)* overall: 1.7 (0.16–19)	24	Personal exposure to wood dust measured gravimetrically and with personal data logging, real-time aerosol monitor; sampling time: 8 hours;
Kalliny *et al.* (2008) Wood-processing plants USA 1999–2004	Sawmill, plywood assembly plants, secondary wood milling operations, factories producing finished wood products	*Geometric mean (GSD)* Inhalable: 1.44 (2.67) Thoracic: 0.35 (2.65) Respirable: 0.18 (2.54)		Size-fractionated dust exposure surveyed longitudinally in 10 wood processing plants across the USA; dust exposures measured using the RespiCon Personal Particle Sampler; woods processed included softwoods (e.g. southern yellow pine and Radiata pine), hardwoods (red oak, maple, poplar, birch, rubber tree wood, cherry), engineered woods (medium-density fibreboard, particleboard), and plywood (from southern yellow pine)
Teschke *et al.* (1999a) Misc. establishments USA 1979–97		*Geometric mean (GSD)*	1632 personal TWA samples	Analysis of 1632 measurements of airborne wood dust reported to OSHA's Integrated Management Information System and development of an empirical predictive model; measurements collected using OSHA sampling method for "total" particulate (i.e. non-specific gravimetric method)
	Overall	1.86 (6.82)		
	Sanders, transportation equipment industry	17.5 (1.79)		
	Press operators, wood products industry	12.3 (4.12)		
	Lathe operators, furniture industry	7.46 (4.56)		
	Sanders, wood cabinet industry	5.83 (5.19)		

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of wood dust (mg/m³)	Number of samples	Comments
Commonwealth of Australia (2008) Wood industries Australia	All wood industries	*Arithmetic mean (range)* 5.8 (0.06–210)	521	Analysis of existing surveillance data on inhalable wood dust exposure; data gathered via a review of published Australian literature; requests to government agencies, consultants, industry associations, specific industries and researchers; telephone surveys, and new air sampling
Alwis *et al.* (1999); Mandryk *et al.* (1999) Wood industries New South Wales, Australia 1996–97		*Geometric mean (GSD)* Inhalable dust		Personal inhalable and respirable samples collected; sampling time: 6–8 hours
	Logging	0.6 (1.3)	7	
	Sawmill	1.6 (3.2)	93	
	Wood chipping	1.9 (1.7)	9	
	Joinery	3.7 (3.7)	66	
		Respirable dust		
	Logging	< 0.1 (1.3)	4	
	Sawmill	0.3 (2.2)	31	
	Wood chipping	0.3 (1.7)	4	
	Joinery	0.5 (1.7)	39	
Scarselli *et al.* (2008) Wood industries Italy 1996–2006	All wood-related	*Geometric mean (GSD)* 1.0 (1.6)	10837	Analysis of airborne wood dust exposure measurements contained in the SIREP (Italian Information System on Occupational Exposure to Carcinogens) database; 10837 measurements on 10528 workers at 1181 companies; concentration of wood dust (hardwood or mixed wood dust) measured as 8-h TWA; no information about type of sample (personal vs stationary) or sampling strategy (random vs systematic)
Baran & Teul (2007) Wood processing Poland	Sawmill, manufacturing frames for furniture, and manufacturing ready-made furniture	*Range* 0.59–16.2		Analysis of measurements on 1100 workers employed in 9 wood-processing plants: 2 sawmills, 4 plants manufacturing frames for upholstered furniture, and 3 plants manufacturing ready-made furniture

Table 1.3 (continued)

Reference, industry and country, period (if reported)	Site, occupation, or exposure circumstance	Concentration of wood dust (mg/m³)	Number of samples	Comments
HSE (2000); Black *et al.* (2007) Woodworking United Kingdom 1999–2000	Sawmilling, joinery, furniture manufacture, other	*Range of medians* 1.5–2.8	396	Cross-sectional survey of 46 representative companies in the British woodworking industry; personal samples collected as per MDHS 14/3; sampling time: 3–6 hours during activities judged to be representative of whole shift; gravimetric analysis of inhalable dust
Spee *et al.* (2007) Building projects the Netherlands 2002	Carpenters	*Geometric mean (GSD)*		Task-based exposure survey of 26 carpenters at 13 building projects from 12 companies; personal and area samples randomly collected as per specially designed protocol for sampling of wood dust in carpentry and furniture industry; gravimetric analysis of wood dust
	- overall	3.3 (2.1)	44	
	Task-based	*Arithmetic mean*		
	- working indoors	5.2	29	
	- working outdoors	2.2	11	
	- indoors + outdoors	16.2	4	

GSD, geometric standard deviation; NR, not reported; OSHA, Occupational Safety and Health Administration; TWA, time-weighted average

was higher for sanding MDF when compared with sanding either hardwood or softwood. However, there was no significant difference with sanding MDF and natural woods, in terms of the quantity of dust generated.

Additional information on the particle size distribution of wood dust in workroom air can be found in the previous *IARC Monograph* (IARC, 1995).

1.2.4 Exposure to other agents

Within the furniture-manufacturing industry, exposure may occur to solvents and formaldehyde in glues and surface coatings. Such exposures are usually greatest for workers with low or negligible exposure to wood dust, and are infrequent or low for workers with high exposure to wood dust. Some outdoor furniture has also been manufactured from impregnated wood containing copper–chromium–arsenic compounds. Formaldehyde-based glues and varnishes were introduced in the wood industry after World War II but they became commonly used only in the 1950s and 1960s in most countries.

The manufacture of plywood and particle board may result in exposure to formaldehyde, solvents, phenol, wood preservatives, and engine exhausts. Sawmill workers may also be exposed to wood preservatives and fungal spores. Wood preservatives used include chlorophenol salts in sawmills, and organochlorine pesticides in plywood mills. When coniferous trees are sawn, monoterpenes evaporate into workroom air. In some sawmills, wood is also impregnated with copper–chromium–arsenic salts or creosote. Construction woodworkers may be exposed to asbestos and silica in their work environment. Many of them also varnish wooden floors with solvent- or water-based varnishes, some of which may release formaldehyde. Exposures to chemicals in industries where other wood products are manufactured vary, but are in many cases similar to those in the furniture-manufacturing industry (IARC, 1995).

1.2.5 Exposure of the general population

Woodworking is a popular hobby and non-occupational exposure may also occur during building and repair operations in homes. Woodworking can encompass a variety of activities that generate wood dust, including sawing, sanding, planing, routing, etc. The woods worked include a variety of particle boards, soft timbers, treated pine, masonite, plywood, and various imported hardwoods and softwoods. The size of the dust particles produced, the amount of dust, and resultant exposure to the person working in these areas depends on several factors including the equipment being used, the ventilation and extraction system in place, the state and type of timber, the general ventilation in the area, and any personal protective equipment that may be used. Exposure levels during non-occupational woodworking may be similar to those at workplaces, but the duration of exposure is usually substantially shorter.

2. Cancer in Humans

In the previous *IARC Monograph*, the evidence associated with exposure to wood dust or wood-related occupations or activites and cancer of the nasal cavity and paranasal sinuses (referred to below as 'sinonasal cancer'), and of the nasopharynx, larynx, lung, stomach, colon, and rectum as well as leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and multiple myeloma was systematically reviewed because excesses had been observed in one or more studies. The Working Group for the previous *IARC Monograph* concluded that there was very strong evidence for sinonasal cancer. In case–control studies, they also consistently observed associations between exposure to wood

dust and cancer of the nasopharynx, but could not rule out confounding; and between wood dust and cancer of the larynx, but noted conflicting evidence from cohort studies. The Working Group concluded that there was "no indication that occupational exposure to wood dust has a causal role in cancers of the oropharynx, hypopharynx, lung, lymphatic and haematopoietic systems, stomach, colon, or rectum" (IARC, 1995).

Since the previous *IARC Monograph*, several studies have been published including selected case series of sinonasal cancer (see Table 2.1), cohort studies (see Table 2.2), registry-based studies (see Table 2.3). For case–control or other studies focused on particular cancer sites, only studies published since the previous volume that reported results for wood dust exposure are summarized here. The results of case–control studies on sinonasal, pharyngeal, and laryngeal cancer are summarized in Tables 2.4, 2.5, and 2.6, respectively. In addition, the results of case–control studies on lung cancer are summarized in Table 2.7, because of the relatively large number of studies that focus on this cancer site. Studies of other cancer sites are summarized in Table 2.8.

2.1 Sinonasal cancer

The Working Group for the previous *IARC Monograph* (IARC, 1995*)* reviewed a large number of case–control studies that consistently observed a strong association between exposure to wood dust or employment in wood-related occupations and sinonasal cancer. Support for this association was found in several large cohort studies of furniture workers (Olsen & Sabroe, 1979; Acheson *et al.*, 1984), but most cohort studies had little power to examine the risks for this cancer site (see Table 18, IARC, 1995). Odds ratios for all or unspecified sinonasal cancers were consistently elevated in case–control studies conducted in many countries (see Table 20, IARC, 1995).

Very high odds ratios were observed for sinonasal adenocarcinoma and strong evidence of a exposure–response relationship was observed in some studies (Hayes *et al.*, 1986; Olsen & Asnaes, 1986; Luce *et al.*, 1993) (see Table 21, IARC, 1995). In addition, an unusually large proportion of all adenocarcinomas in cases series were woodworkers. Some case–control studies observed an excess risk of sinonasal squamous cell carcinoma associated with wood dust or wood occupations, but the association was much weaker than was observed with adenocarcinoma (see Table 22, IARC, 1995). A pooled re-analysis of 12 case–control studies (including six of the nine above) found strong evidence for a exposure–response relationship among men for adenocarcinoma (OR, 0.6; 95%CI: 0.6–4.7 for low; OR, 3.1; 95%CI: 1.6–6.1 for moderate; and OR, 45.5; 95%CI: 28.3–72.9 for high wood dust), and little evidence for squamous cell carcinoma (OR, 0.9; 95%CI: 0.6–1.2 for low; OR, 1.0; 95%CI: 0.7–1.4 for moderate; and OR, 0.8; 95%CI: 0.4–1.6 for high wood dust) (Demers *et al.*, 1995a). For the three studies with results for squamous cell carcinoma not included in the pooled re-analysis, Fukuda *et al.* (1987) observed an excess among both male (OR, 2.9; 95%CI: 1.5–5.6) and female woodworkers (OR, 2.0; 95%CI: 0.3–14), Shimizu *et al.* (1989) observed an excess of squamous cell carcinoma of the maxillary sinus among male woodworkers (OR, 2.1; 95%CI: 0.8–5.3), and Olsen & Asnaes (1986) observed only a slightly increased risk of carcinoma of the sinonasal cavities among men classified as exposed to wood dust (OR, 1.3; 95%CI: 0.6–2.8).

Among the cohort studies that reported tree species, an excess of sinonasal cancer (SMR, 8.1; 95%CI: 3.7–16) was observed among British furniture workers exposed to hardwood dust (Rang & Acheson, 1981; Acheson *et al.*, 1984). No cases of sinonasal cancer were reported in a much smaller study of German furniture

workers exposed to beech, oak, and pine (Barthel & Dietrich, 1989) or among two small cohort of workers exposed to softwood—Finnish sawmill workers (Jäppinen *et al.*, 1989) and American plywood workers (Robinson *et al.*, 1990). [The Working Group noted that their power to detect an excess was low, and that exposure levels among sawmill and plywood workers were low compared to furniture workers.]

Few case–control studies in the previous *IARC Monograph* reported tree species. Very large excesses of sinonasal adenocarcinoma were associated with hardwood dust exposure in studies from France (OR, 5.30; 95%CI: 1.04–2.70, for highest level of exposure, Leclerc *et al.*, 1994) and Italy (OR, 0.90; 95%CI: 0.20–4.07, Battista *et al.*, 1983). Excesses of sinonasal cancer were observed among workers primarily exposed to softwood in case–control studies from Nordic Countries (OR, 3.3; 95%CI: 1.1–9.4, Hernberg *et al.*, 1983), the USA (OR, 3.1; 95%CI: 1.0–9.0 with 15-year lag, Vaughan *et al.*, 2000), Canada (OR, 2.5; $P < 0.03$, Elwood, 1981), and France (OR, 1.7, Leclerc *et al.*, 1994). The results for three of these four studies were restricted to squamous cell carcinoma.

Early case series reported many cases of sinonasal adenocarcinoma that were exposed to hardwoods (Acheson *et al.*, 1968, 1972; Leroux-Robert, 1974; Luboinski & Marandas, 1975; Andersen *et al.*, 1976, 1977; Engzell *et al.*, 1978; Kleinsasser & Schroeder, 1989). Seven cases of sinonasal squamous cell carcinoma exposed to “softwoods” were reported in a Norwegian case series (Voss *et al.*, 1985), and three cases of adenocarcinoma were reported among British workers exposed to softwoods (Acheson *et al.*, 1972). Several new case series have also been published with results relevant for the evaluation of sinonasal cancer (Table 2.1). Case series of sinonasal adenocarcinoma continue to make up a large proportion of cases with exposure to wood dust, with mean exposure durations ranging from 25 to 37 years. Most case series were restricted to adenocarcinoma, but in the case series that considered other tumours, the proportion of wood dust exposure was much less in the non-adenocarcinoma cases.

In the period following the previous *IARC Monograph* (IARC, 1995), five cohort studies (Table 2.2) were published that are relevant for the evaluation of wood dust, and three present results for sinonasal cancer. In a pooled re-analysis of five previously published cohort studies, Demers *et al.* (1995b) found an excess risk of sinonasal cancer among men classified as being definitely exposed to wood dust (SMR, 8.4; 95%CI: 3.9–16.0). Stellman *et al.* (1998) found no evidence of an excess risk associated with self-reported wood dust exposure or longest occupation among participants in the Cancer Prevention Study II. Innos *et al.* (2000) found an excess risk of sinonasal cancer among Estonian furniture workers highly exposed to wood dust (for men SIR, 2.3; 95%CI: 0.3–8.4, $n = 2$; for women SIR, 3.2; 95%CI: 0.1–18.1, $n = 1$).

Three new case–control studies (Table 2.4) have published results relevant for the evaluation of sinonasal cancer. Teschke *et al.* (1997) found no association with softwood or hardwood dust in a small Canadian study. In a pooled re-analysis of European case–control studies ’t Mannetje *et al.* (1999) found a strong association with adenocarcinoma (OR, 12.2; 95%CI: 7.4–20.0), but no association with squamous cell carcinoma (OR, 0.7; 95%CI: 0.5–1.1). Pesch *et al.* (2008) found a strong association between adenocarcinoma and hardwood dust exposure (OR, 4.0; 95%CI: 1.9–8.3), but not with softwood dust exposure (OR, 0.3; 95%CI: 0.2–0.7). [The Working Group noted that only compensated cases were included, and this may have biased the results towards hardwood dust exposure.]

Table 2.1 Case series of sinonasal cancer according to occupation and exposure to wood dust

Reference, location, name of study	Sex	Origin	Histology	Exposed cases/ total cases	Occupations/exposures	Comments
Svane-Knudsen *et al.* (1998) Denmark	M, F	Nasal cavity and paranasal sinuses Hospital-based series 1978–95	Adenocarcinomas Epidermoid carcinomas	12/22 3/41	Hardwood dust exposure based on patient records [further details were not provided]	Softwood dust exposure not mentioned
Stoll *et al.* (2001) France	M, F	Ethmoidal sinuses 1975–2000	Adenocarcinomas	62/76	Exposed to wood dust	Mean duration of wood dust exposure 26 yr
Roux *et al.* (2002) France		Sinonasal cancer 1985–2001	Adenocarcinomas	134/139	Wood dust exposure from furniture, sawmill, carpentry and wood-product workers	Mean duration of wood dust exposure 30 yr
Barbieri *et al.* (2005) Italy	M, F	Ethmoidal sinuses 1978–2002	Adenocarcinomas	17/100	Hardwood and softwood dust exposure (5 softwood only)	
Liétin *et al.* (2006) France	M, F	Ethmoidal sinuses Hospital-based series 1985–2004	Adenocarcinomas	45/60	Wood dust exposure	Mean duration of wood dust exposure 25.6, range 2–44 yr
Fontana *et al.* (2008) France	M, F	Sinonasal cancer Diagnostic Registry 1981–2000	All	46/76 men 0/24 women	Wood dust exposure	Mean duration of wood dust exposure 37 yr
Llorente *et al.* (2008) Spain	M, F	Hospital-based series 1986–2002	All	62/79	Wood dust exposure	
Bornholdt *et al.* (2008) Denmark	M, F	Sinonasal cancer 1991–2001	Adenocarcinomas Squamous cell carcinomas	33/58 7/109	Wood dust exposure as per job title from the Central Person Registry or interview	
Choussy *et al.* (2008) France	M, F	Ethmoidal sinuses Hospital-based series 1976–2001	Adenocarcinomas	353/418	Wood dust exposure	Mean duration of wood dust exposure 27.7 yr

Table 2.2 Cohort studies of woodworkers exposed to wood dust

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Demers *et al.* (1995b) Cohort mortality study United Kingdom and USA	Pooled analysis of updated data from 5 studies: British furniture workers (Acheson *et al.*, 1984), US furniture workers (Miller *et al.*, 1994), two cohorts of plywood workers (Blair *et al.*, 1990; Robinson *et al.*, 1995), and wood model makers (Roscoe *et al.*, 1992)	Workers classified as exposed to wood dust based on available work history	All cancers (140–208)	All woodworkers	1726	0.8 (0.8–0.8)	SMRs adjusted for sex, age, & calendar period using national rates	
			Pharynx (146–149)	All woodworkers	20	0.8 (0.5–1.3)		
			Nasopharynx (147)	All woodworkers	9	2.4 (1.1–4.5)		
				Possible wood dust	4	2.9 (0.8–7.5)		
				Probable wood dust	0	0.0 (0.0–3.8)		
				Definite wood dust	5	5.3 (1.7–12.4)		
			Paranasal sinus (160)	All woodworkers	11	3.1 (1.6–5.6)		
				Possible wood dust	1	0.8 (0.0–4.6)		
				Probable wood dust	1	1.2 (0.0–6.5)		
				Definite wood dust	9	8.4 (3.9–16.)		
			Larynx (161)	All woodworkers	18	0.7 (0.4–1.0)		
				Possible wood dust	4	0.4 (0.1–1.1)		
				Probable wood dust	8	1.1 (0.5–2.1)		
				Definite wood dust	6	0.8 (0.3–1.8)		
			Lung (162)	All woodworkers	575	0.8 (0.7–0.9)		
			Stomach (151)	All woodworkers	138	0.9 (0.8–1.1)		
			Intestine (152, 153)	All woodworkers	136	0.8 (0.6–0.9)		
			Rectum (154)	All woodworkers	60	0.8 (0.6–1.0)		
			Non-Hodgkin lymphoma (200, 202)	All woodworkers	57	1.1 (0.8–1.4)		
			Hodgkin disease (201)	All woodworkers	12	0.6 (0.3–1.1)		
			Multiple myeloma (203)	All woodworkers	33	1.3 (0.9–1.3)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Demers *et al.* (1995b) (contd.)				Possible wood dust	9	1.0 (0.5–1.9)		
				Probable wood dust	8	1.3 (0.6–2.5)		
				Definite wood dust	11	1.6 (0.8–2.8)		
			Leukaemia (204–208)	All woodworkers	47	0.7 (0.5–0.9)		
Stellman *et al.* (1998) Prospective cohort USA	Prospective study of 362823 men enrolled in the American Cancer Society Cancer Prevention Study II in 1982 and followed up for 6 yr	Self-reported wood dust exposure or wood-related occupation	All causes (0–999)	Wood dust exposure	2995	1.1 (1.0–1.1)	RRs adjusted for age and smoking status	
				Wood occupation	1271	1.2 (1.1–1.2)		
			All cancers (140–208)	Wood dust exposure	961	1.1 (1.0–1.2)		
				Wood occupation	381	1.2 (1.1–1.3)		
			Pharynx (146–149)	Wood dust exposure	7	0.9 (0.4–2.0)		
				Wood occupation	2	0.8 (0.2–3.4)		
			Nasopharynx (147)	Wood dust exposure	1	0.4 (0.1–3.3)		
				Wood occupation	1	1.4 (0.4–1.8)		
			Paranasal sinus (160)	Wood dust exposure	1	1.1 (0.1–8.4)		
				Wood occupation	0			
			Larynx (161)	Wood dust exposure	8	1.6 (0.8–3.4)		
				Wood occupation	2	1.2 (0.3–4.9)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Stellman *et al.* (1998) (contd.)			Lung (162)	Wood dust exposure	317	1.2 (1.0–1.3)		
				Wood occupation	111	1.1 (0.9–1.4)		
			Stomach (151)	Wood dust exposure	40	1.3 (1.0–1.9)		
				Wood occupation	11	1.1 (0.6–1.9)		
			Colon (153)	Wood dust exposure	100	1.0 (0.8–1.3)		
				Wood occupation	37	1.0 (0.8–1.5)		
			Rectum (154)	Wood dust exposure	23	1.3 (0.8–2.0)		
				Wood occupation	9	1.5 (0.8–2.9)		
			Non-Hodgkin lymphoma (200, 202)	Wood dust exposure	39	1.1 (0.8–1.5)		
				Wood occupation	12	1.0 (0.6–1.7)		
			Hodgkin disease (201)	Wood dust exposure	4	1.2 (0.4–3.4)		
				Wood occupation	1	1.0 (0.1–7.7)		
			Multiple myeloma (203)	Wood dust exposure	16	1.0 (0.6–1.8)		
				Wood occupation	4	0.7 (0.3–1.9)		
			Leukaemia (204–208)	Wood dust exposure	32	0.9 (0.6–1.3)		
				Wood occupation	14	1.1 (0.6–1.9)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Innos *et al.* (2000) Retrospective cancer incidence cohort study Estonia	Retrospective study of incident cancers in all furniture workers employed in Tallinn, Estonia, for at least six months between 1 January 1946 and 31 December 1988 and living in Estonia on 1 January 1968. Cancer incidence follow-up: 1968–95	Exposure based on industrial hygiene surveys and work history	All cancers (140–208)	Med. exposure men	55	1.2 (0.9–1.6)	SIRs adjusted for age and calendar period	
				High exposure men	265	1.0 (0.9–1.1)		
				Med. exp. women	98	1.0 (0.8–1.2)		
				High exposure women	171	1.1 (0.9–1.3)		
			Buccal cavity (140–145)	Med. exposure men	5	3.7 (1.2–8.6)		
				High exposure Men	6	0.8 (0.3–1.7)		
				Med. exp. women	2	2.5 (0.3–8.9)		
				High exposure women	2	1.6 (0.2–5.8)		
			Pharynx (146–149)	Med. exposure men	3	4.0 (0.8–11.8)		
				High exposure men	6	1.5 (0.6–3.3)		
				Med. exposure women	0	0.0		
				High exposure women	0	0.0		
			Paranasal sinus (160)	Med. exposure men	0	0.0		
				High exposure men	2	2.3 (0.3–8.4)		
				Med exposure women	0	0.0		
				High exposure women	1	3.2 (0.1–18.1)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Innos *et al.* (2000) (contd.)			Larynx	Men	7	0.7 (0.3–1.4)		
				Women	1	1.7 (0.0–9.4)		
			Bronchi and lung (162)	Med. exposure men	9	0.8 (0.4–1.5)		
				High exposure men	70	1.0 (0.8–1.3)		
				Med. exposure women	5	1.1 (0.4–2.6)		
				High exposure women	11	1.6 (0.8–2.9)		
			Stomach (151)	Med. exposure men	11	1.7 (0.9–3.0)		
				High exposure men	36	0.9 (0.6–1.2)		
				Med. exposure women	13	1.2 (0.7–2.1)		
				High exposure women	23	1.4 (0.9–2.1		
			Colon (153)	Med. exposure men	6	3.0 (1.1–6.7)		
				High exposure men	18	1.5 (0.9–2.4)		
				Med. exposure women	8	1.4 (0.6–2.7)		
				High exposure women	16	1.8 (1.0–2.9)		
			Rectum (154)	Med. exposure men	1	0.6 (0.0–3.2)		
				High exposure men	13	1.2 (0.7–2.1)		
				Med. exposure women	7	1.6 (0.6–3.2)		
				High exposure women	11	1.6 (0.8–2.9)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Innos *et al.* (2000) (contd.)			Hodgkin disease (201)	Med. exposure men	1	2.6 (0.1–14.3)		
				High exposure men	3	1.4 (0.3–4.2)		
				Med. exposure Women	0	0.0		
				High exposure women	1	1.3 (0.0–7.5)		
			Haematopoietic and lymphatic (200–208)	Med. exposure men	2	0.8 (0.1–2.8)		
				High exposure men	14	0.9 (0.5–1.5)		
				Med. exposure women	5	1.0 (0.3–2.3)		
				High exposure women	3	0.4 (0.1–1.2)		
Szadkowska-Stańczyk & Szymczak (2001) Nested case–control study Poland	79 deceased lung cancer cases from a cohort of 10575 Polish pulp and paper mill workers (7084 men, 3491 women), 1+ yr, 1968–90, observed through 1995	Employment history obtained from the mills; occupational exposure was assessed by experts and a cumulative dose index	Lung (162)	Wood dust exposure	10	2.1 (0.9–4.9)	ORs adjusted for smoking. Matched on sex, birth year (± 1 yr), hire year (± 3 yr), and vital status	
				Low	4	2.1 (0.6–7.4)		
				Moderate & high	6	2.1 (0.7–6.3)		
				1–4 yr of exposure	4	1.7 (0.5–6.2)		
				5+ yr of exposure	6	2.4 (0.8–7.7)		
				Low cumulative dose	4	2.1 (0.5–9.2)		
				High cumulative dose	6	2.0 (0.7–5.4)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Dement *et al.* (2003) Cohort mortality study USA	13354 male carpenter members of the United Brotherhood of Carpenters and Joiners of America matched to the New Jersey State Cancer registry, who had participated in the New Jersey Carpenters fund before 1 July 2000 and matched to the New Jersey Carpenters Pension Fund All incident cancer cases within the cohort 1979–2000	Employment as a carpenter	All cancers (140–208)	All	592	1.1 (1.0–1.2)	SIRs adjusted for age and calendar period	The lowest duration of carpenter work (< 10 yr) was used as the comparison group for expected cases
			Pharynx (146–149)		11	1.4 (0.7–2.4)		
			Oesophagus (150)		8	1.1 (0.5–2.2)		
			Stomach (151)		12	1.0 (0.5–1.8)		
			Rectum (154)		35	1.5 (1.1–2.1)		
			Liver and gallbladder (155, 156)		12	1.6 (1.1–2.1)		
			Larynx (161)		14	1.2 (0.7–2.0)		
			Trachea, bronchus, and lung (160, 162)		137	1.5 (1.2–1.7)		
			Other respiratory (163–165)		15	4.2 (2.4–6.9)		
			Leukaemia (204–208)		12	0.8 (0.4–1.4)		
			Myeloma (203)		9	1.5 (0.7–2.8)		
Lee *et al.* (2003) Cohort cancer incidence study Sweden	365424 male construction workers screened by the Organization for Working Environment, Occupational Safety and Health during 1971–93 and followed during 1971–99 through the Swedish National Cancer Registry	Wood dust exposure assessment based on a job–exposure matrix	Multiple myeloma (203)	Never exposed[1]	376	1.0 (reference)	RR[1] adjusted for BMI at entry to cohort	
				Ever exposed[1]	20	0.8 (0.49–1.20)		
				Never exposed[2]	376	1.0 (reference)	RR[2] adjusted for age, BMI, and other occupational co-exposures	
				Ever exposed[2]	20	0.8 (0.49–1.23)		

Table 2.2 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Jansson *et al.* (2005) Cohort cancer incidence study Sweden	Male construction workers, same population as Lee *et al.* (2003) 260052 workers in cohort after excluding those missing smoking and BMI	Wood dust exposure assessment based on a job–exposure matrix	Oesophogus (adenocarcinoma)	No exposure	61	1.0 (reference)	IRRs adusted for attained age, calendar year at entry into cohort, tobacco smoking at entry to cohort and BMI at entry to cohort	
				Moderate exposure	3	0.8 (0.2–2.5)		
				High exposure	0	0		
			Gastric (cardia; adenocarcinoma)	No exposure	152	1.0 (reference)		
				Moderate exposure	11	1.1 (0.6–2.0)		
				High exposure	2	4.8 (1.2–19.4)		
			Oesophagus (squamous cell carcinoma)	No exposure	170	1.0 (reference		
				Moderate exposure	8	0.7 (0.4–1.5)		
				High exposure	1	2.2 (0.3–15.9)		
Purdue *et al.* (2006) Cohort cancer incidence study Sweden	Male construction workers, same population as Lee *et al.* (2003). 307779 workers in cohort after excluding those missing smoking	Wood dust exposure assessment based on a job–exposure matrix	All sites (140–208)	Never exposed	490	1.0	RRs adjusted for age, smoking status and snuff use	
				Ever exposed	20	0.7 (0.4–1.0)		
			Oral cavity (140–145)	Never exposed	166	1.0		
				Ever exposed	5	0.5 (0.2–1.2)		
			Pharynx (146–149)	Never exposed	108	1.0		
				Ever exposed	4	0.6 (0.2–1.6)		
			Larynx (161)	Never exposed	216	1.0		
				Ever exposed	11	0.8 (0.5–1.5)		
Sjödahl *et al.* (2007) Cohort cancer incidence study Sweden	Male construction workers, same population as Lee *et al.* (2003). 256357 workers in cohort after excluding those missing smoking and BMI	Wood dust exposure assessment based on a job–exposure matrix	Gastric (non-cardia) (151)	Wood dust			RRs adjusted for age, smoking status and BMI	
				No exposure	892	1.0 (reference)		
				Moderate exposure	53	0.9 (0.7–1.2)		
				High exposure	3	1.2 (0.4–3.6)		

BMI, body mass index; CI, confidence interval; IRR, incidence rate ratio; RR, relative risk; SIR, standardized incidence ratio; standardized mortality ratio; yr, year or years

Table 2.3 Descriptive and linkage studies with results on exposure to wood dust

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Pukkala *et al.* (2009) Census cancer incidence linkage Nordic countries	All incident cancer cases diagnosed in Denmark (1961–2005), Finland (1961–2005), Norway (1961–2005), Sweden (1961–2005) and Iceland (1961–2005)	Woodworkers includes workers who prepare and treat wood and make, assemble and repair constructions and products of wood	All cancers (140–208)	Men	74353	0.95 (0.95–0.96)	SIRs adjusted for age and calendar period	National rates use to calculate expected cancers
				Women	3004	0.92 (0.89–0.95)		
			Pharynx (146–149)	Men	450	0.83 (0.76–0.11)		
				Women	8	0.94 (0.4–1.9)		
			Nose (160)	Men	355	1.8 (1.7–2.04)		
				Women	10	1.9 (0.9–3.5)		
			Adenocarcinoma	Men	122	5.5 (4.6–6.6)-		
				Women				
			Larynx (161)	Men	819	0.82 (0.77–0.8)		
				Women	7	1.7 (0.5–3.9)		
			Lung (162)	Men	10941	0.96 (0.94–0.97)		
				Women	235	1.2 (1.1–1.4)		
			Mesothelioma (158, 162.2)	Men	494	1.6 (1.4–1.7)		
				Women	11	2.1 (1.1–3.8)		
			Stomach (151)	Men	4904	1.04 (1.01–1.07)		
				Women	133	1.1 (0.93–1.3)		
			Colon (153)	Men	5478	0.9 (0.88–0.93)		
				Women	206	0.88 (0.77–1.01)		
			Rectum (154)	Men	3988	0.97 (0.94–1.0)		
				Women	123	0.96 (0.8–1.14)		
			Hodgkin disease (201)	Men	382	1.04 (0.94–1.15)		
				Women	5	0.47 (0.15–1.11)		
			Non-Hodgkin lymphoma (200, 202)	Men	2170	0.97 (0.933–1.02)		
				Women	110	1.03 (0.85–1.24)		
			Multiple myeloma (203)	Men	1263	1.01 (0.96–1.07)		
				Women	47	1.03 (0.76–1.37)		
			Leukaemia (204)	Men	1898	0.96 (0.92–1.01)		
				Women	61	0.93 (0.71–1.19)		

Table 2.3 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Weiderpass *et al.* (2001) Census linkage study Finland	2833 cases of endometrial cancers and 1101 cervical cancers diagnosed since 1971 in a cohort of 413877 skilled and specialized workers in Finland excluding farming occupations	Occupations were coded into job titles and a national job–exposure matrix (FINJEM) converted each job title into a probability and mean level of exposure	Endometrium	Wood surface finisher	8	1.8 (0.8–3.5)	SIRs adjusted for birth cohort, follow-up period, and social class	
				Low wood dust exposure	368	1.0 (0.9–1.2)		
			Cervix	High wood dust exposure	70	1.1 (0.8–1.4)		
				Woodworker, NEC	7	2.5 (1.0–5.1)		
				Plywood and fibreboard worker	24	1.6 (1.0–2.3)		
				Low wood dust exposure	249	1.2 (1.0–1.4)		
				High wood dust exposure	34	1.2 (0.9–1.7)		

Table 2.3 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Arias Bahia *et al.* (2005) Registry-based study Brazil	138 male cases in wood-related jobs based on hospital records, 1991–99, 20+ yr of age Expected numbers based on male incident rates from the Belem population-based cancer registry. 2420 deaths among woodworkers compared to other deaths in the State of Para	Employment as a wood worker	Oral cavity and pharynx		8	1.7 (1.0–2.6)	Age	PCIRs – proportional cancer incidence ratios Belem (1988–89)
			Stomach		32	1.0 (0.7–1.5)		
			Colon		1	0.3 (0.0–1.7)		
			Rectum		3	1.1 (0.2–3.7)		
			Nasal cavity		1	1.5 (0.0–8.5)		
			Larynx		7	1.2 (0.5–2.4)		
			Lung		18	1.2 (0.7–1.9)		
			Hodgkin disease		3	2.2 (0.4–6.3)		
			Other lymphomas		0	0.0		
			Multiple myeloma		2	2.4 (0.3–8.8)		
			Leukaemia		4	1.4 (0.4–3.5)		
			Oral cavity and pharynx		18	1.0 (0.6–1.7)		CMORs – cancer mortality odds ratios State of Para (1980–95)
			Stomach		82	0.8 (0.7–1.1)		
			Colon		5	0.5 (0.2–1.2)		
			Rectum		8	1.3 (0.6–2.8)		
			Larynx		18	1.3 (0.6–2.8)		
			Lung		53	0.8 (0.6–1.0)		
			Hodgkin disease		5	1.1 (0.4–2.8)		
			Other lymphomas		11	1.4 (0.7–2.6)		
			Multiple myeloma		1	0.5 (0.0–3.4)		
			Leukaemia		7	0.6 (0.2–1.2)		

Table 2.3 (continued)

Reference, location, name of study	Cohort description	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	RR (95%CI)*	Adjustment for potential confounders	Comments
Laakkonen et al. (2006) Census linkage study Finland	Incident cancer cases in all economically active Finns born during 1906–45 who participated in the national population census on 31 December 1970 (667121 men; 513110 women)	Exposure to wood dust: None (0) Low (< 3 mg/ m^3–yr) Med (3–50 mg/ m^3–yr) High (> 50 mg/ m^3–yr)	Nasal cavity (160)	None men	259	1.0 (0.9–1.1)	SIRs adjusted for age and social class	Exposure lag period 20 yr
				women	118	1.0 (0.8–1.2)		
				Low men	15	1.6 (0.9–2.6)		
				women	1	1.7 (0.0–9.7)		
				Med men	17	1.3 (0.8–2.1)		
				women	1	0.8 (0.0–4.4)		
				High men	1	1.2 (0.0–6.9)		
				women	0	0.0		
			Larynx (161)	None men	1965	1.0 (1.0–1.1)		
				women	128	1.0 (0.8–1.2)		
				Low men	76	1.1 (0.8–1.3)		
				women	1	1.2 (0.0–6.8)		
				Med men	77	0.7 (0.6–0.9)		
				women	3	2.1 (0.4–6.1)		
				High men	1	0.1 (0.0–0.7)		
				women	0	0.0		
			Lung (162)	None men	27309	1.0 (1.0–1.0)		
				women	3446	1.0 (1.0–1.0)		
				Low men	936	1.1 (1.0–1.2)		
				women	21	0.9 (0.6–1.4)		
				Med men	1784	1.0 (1.0–1.1)		
				women	48	1.0 (0.8–1.4)		
				High men	108	0.9 (0.7–1.0)		
				women	12	1.0 (0.5–1.7)		

CI, confidence interval; CMORs, cancer mortality odds ratios; PCIRs, proportional cancer incidence ratios; RR, relative risk; SIR,standardized incidence ratio; yr, year or years

2.2 Cancer of the nasopharynx

The previous *IARC Monograph* reviewed nine community-based case–control studies of cancer of the nasopharynx (see Table 25, IARC, 1995). The majority indicated an excess risk associated with either wood dust exposure (4/5 studies) or wood-related occupations (3/4 studies). Many of these studies had positive results based on very small numbers, and did not control for confounding. The studies were conducted in many different countries and odds ratios were generally in the range of 1.5–2.5. Among the studies that adjusted for the effects of smoking and alcohol, Vaughan (1989) and Vaughan & Davis (1991) observed an excess risk among carpenters (OR, 4.5; 95%CI: 1.1–19), and all woodworkers employed for 10 years or longer (OR, 4.2; 95%CI: 0.4–27). Sriamporn *et al.* (1992) observed an excess risk among wood cutters (OR, 4.1; 95%CI: 0.8–22).

None of the cohort studies reviewed by the previous *IARC Monograph* provided results for cancer of the nasopharynx, a rare tumour with an incidence rate of approximately 1/100000 in European countries.

In the period following the previous *IARC Monograph* (IARC, 1995), five new or updated cohort studies (Table 2.2) were published including a pooled re-analysis of five previously published cohort studies. Demers *et al.* (1995b) found an excess risk of cancer of the nasopharynx among workers classified as definitely exposed to wood dust (SMR, 5.3; 95%CI: 1.7–12.4, $n = 5$) and, overall, excesses were observed among both furniture (SMR, 2.4; 95%CI: 1.2–5.9, $n = 7$) and plywood workers (SMR, 4.6; 95%CI: 0.6–16.4, $n = 2$). Stellman *et al.* (1998) found no evidence of an excess risk associated with self-reported wood dust exposure or longest occupation among participants in the Cancer Prevention Study II. The remaining cohort studies did not present results for this organ site.

Three new case–control studies (Table 2.5) have published results relevant for the evaluation of cancer of the nasopharynx. Armstrong *et al.* (2000) observed an increased risk associated with wood dust among Malaysian Chinese workers (OR, 2.4; 95%CI: 1.3–4.2). Vaughan *et al.* (2000) in a population-based study observed no increased risk overall (OR, 1.2; 95%CI: 0.5–2.7), and no evidence of an exposure–response relationship in analyses by maximum or cumulative exposure in a multicentre study in the USA. In another population-based study Hildesheim *et al.* (2001) found an increased risk overall (OR, 1.7; 95%CI: 1.0–3.0), which increased with both duration and cumulative exposure in Taiwan, China. It was also reported that these results were not affected by further adjustment for formaldehyde. One further hospital-based study reported an excess for nasopharyngeal and sinonasal cancer combined (Jayaprakash *et al.*, 2008).

2.3 Cancer of the pharynx

The previous *IARC Monograph* reviewed four case–control studies of cancer of the pharynx other than the nasopharynx (see Table 26, IARC, 1995). Two indicated an excess risk associated with wood-related occupations, although one was based on very small numbers. Another found mixed evidence. None of the cohort studies reviewed by that Working Group provided relevant results.

Four new case–control studies (Table 2.5) published since the previous *IARC Monograph* have results relevant for the evaluation of cancer of the pharynx other than the nasopharynx. Gustavsson *et al.* (1998) observed a decreased risk for cancer of the hypopharynx associated with wood dust in Sweden (OR, 0.5; 95%CI: 0.3–1.0). Laforest *et al.* (2000) observed no increased risk overall (OR, 0.9; 95%CI: 0.5–1.7), and only a slightly increased risk in the highest categories of cumulative exposure (OR, 1.5; 95%CI: 0.6–3.9). Berrino *et al.* (2003) found an increased risk of

Table 2.4 Case–control studies of sinonasal cancer and exposure to wood dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Teschke *et al.* (1997) Population-based case–control study Canada	Nasal cavity and paranasal sinus (160)	All incident cases with histologically confirmed primary malignant tumours age ≥ 19 yr; 1990–92	Controls were selected randomly from 5-yr age and sex strata of the provincial voters list; frequency-matched for age and sex	Occupational histories obtained by interview and occupational exposures assessed by job classification	Hardwood dust Softwood dust	0.6 (0.1–3.0) 0.7 (0.3–1.6)	Sex, age (< 60, 60–69, ≥ 70), cigarette smoking (0–19, ≥ 20 pack–years)	
't Mannetje *et al.* (1999) Pooled population-based case–control study Italy, France, Netherlands, Germany, Sweden	Nasal cavity and paranasal sinus (160)	555 cases (104 women, 451 men) from 4 studies in Italy and 1 each from the Netherlands, France, Germany, and Sweden	1705 controls (241 women, 1464 men) from the same studies	Occupational history and job–exposure matrices were applied for wood dust	Wood dust exposure: Women Men Adenocarcinoma Squamous cell carcinoma	 1.2 (0.3–4.5) 2.4 (1.8–3.2) 12.2 (7.4–20.0) 0.7 (0.5–1.1)	Age group and study centre. Sex and smoking where applicable	
Pesch *et al.* (2008) Industry-based case–control study Germany	Nasal cavity and paranasal sinus (160)	86 male cases of adenocarcinoma of the nasal cavity and paranasal sinuses identified among workers with a recognized occupational disease during 1994–2003	204 controls randomly recruited from recognized accidents and falls frequency-matched to controls for age with 60 yr cut-off. Controls were also employed in the woodworking industries	Cumulative and average wood dust exposure quantified with a job–exposure matrix based on wood dust measurements at recent and historical workplaces	High exposure to: Hardwood Softwood Particle board Medium-density fibreboard	 4.0 (1.9–8.3) 0.3 (0.2–0.7) 0.5 (0.3–1.0) 0.3 (0.1–1.1)	Smoking, age, region, ever exposed to varnishes or stains	Only cases with successful compensation claims were used

Table 2.5 Case–control studies of cancer of the pharynx and exposure to wood dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Gustavsson *et al.* (1998) Population-based case–control study Sweden	Pharynx (140–149)	401 incident squamous cell carcinomas, men aged 40–79 yr living in Stockholm or Southern health care region, 1988–91	Randomly selected from the base population, frequency-matched on region and age group	Occupational history, exposure assessment based on literature survey of exposure	Ever exposed	0.5 (0.3–1.0)	Region, age, alcohol consumption, smoking habits	
Armstrong *et al.* (2000) Population-based case–control study Malaysia	Nasopharynx (147)	282 Chinese cases identified between July 1990 and June 1992 through diagnosis records and/or treatment at centres with radiotherapy in the study area of Selangor & the Federal Territory	Matched by age (± 3yr) to 1 control in good health with no history of cancer of the head, neck or respiratory system, selected from Chinese population	Occupational histories were obtained by interview, exposure based on job	Any history of occupational exposure to wood dust	2.4 (1.3–4.2)	Diet and cigarette smoke indices, and matched on age	
Vaughan *et al.* (2000) Multicentred population-based case–control study USA 1987–93	Nasopharynx (147)	196 newly diagnosed cases in men & women, age 18–74 yr, from 5 registries (Connecticut, Detroit, Iowa, Utah and western Washington)	244 controls from the general population through random-digit dialling and frequency-matched to the cases by age (± 5yr), sex and cancer registry	Lifetime histories of occupational and chemical exposures taken by interview; estimates of exposures assessed on a job-by-job basis	Ever exposed Max exposure (mg/m^3): > 0.0–0.55 > 0.55–1.50 > 1.50 Cumulative (mg/m^3–yr): > 0.0–2.75 > 2.75–15.70 > 15.70	1.2 (0.5–2.7) 1.3 (0.5–3.6) 2.0 (0.5–8.1) 0.2 (0.0–2.1) 0.7 (0.2–2.5) 3.0 (0.9–9.8) 0.4 (0.1–2.3)	Age, sex, race, SEER site, cigarette use, proxy status, education and cumulative exposure to formaldehyde	

Table 2.5 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Laforest *et al.* (2000) Hospital-based case–control study France 1989–91	Hypopharynx (148)	296 men, incident squamous cell carcinomas, histologically confirmed from 15 hospitals	Controls were patients with primary cancers of different sites requiring the same medical environment as case cancers, frequency-matched on age, same hospital or similar hospitals nearby, 1987–91	Detailed lifetime occupational history taken, occupational exposures were assessed through a job–exposure matrix	Ever exposed	0.9 (0.2–4.1)	Age, smoking, alcohol, exposure to formaldehyde (yes/no), and mineral fibres (yes/no)	
					Probability:			
					≤ 70%	0.7 (0.3–1.8)		
					> 70%	1.1 (0.5–2.3)		
					Duration:			
					< 6 yr	0.5 (0.2–1.5)		
					6–10 yr	1.0 (0.3–2.9)		
					> 10 yr	1.2 (0.5–3.0)		
					Cumulative:			
					Low (< 10)	0.6 (0.2–1.6)		
					Medium (10–42)	0.7 (0.3–2.3)		
					High (> 42)	1.5 (0.6–3.9)		
Hildesheim *et al.* (2001) Population-based case–control study Taiwan, China July 1991 to December 1994	Nasopharynx (147)	375 newly diagnosed, histologically confirmed cases identified through two tertiary care hospitals in Taipei, Taiwan, China; < 75 yr of age, residents of Taipei city for 6+ mo	325 community controls matched to cases on sex, age and geographic residence by use of listings available through the National Household Registration System	Occupational history via interview, blindly assessed by an industrial hygienist for intensity and probability of exposure	Ever exposed	1.7 (1.0–3.0)	Age, sex, education, ethnicity, and HLA	
					Duration:			
					≤ 10 yr	1.2 (0.6–2.5)		
					> 10 yr	2.4 (1.1–5.0)		
					Cumulative:			
					< 25	1.2 (0.6–2.5)		
					≥ 25	2.4 (1.2–5.1)		

Table 2.5 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Berrino *et al.* (2003) Population-based case–control study Italy, France, Spain, Switzerland 1979–82	Hypopharynx (148)	304 male incident cases from Calvados, France; Turin and Varese, Italy; Pamplona and Zaragoza, Spain; and Geneva, Switzerland	2176 male population controls	Occupational history through specialist interview; exposures assessed using a job–exposure matrix	< 55 yr of age:		Age, centre, tobacco, alcohol, diet, socioeconomic status, and exposure to other agents	
					Possible exposure	0.3 (0.1–1.0)		
					Probable exposure	0.4 (0.2–1.2)		
					> 55 yr of age:			
					Wood dust exposure	2.1 (1.2–3.7)		
Vlajinac *et al.* (2006) Hospital-based case–control study Serbia & Montenegro 1998–2000	Oropharynx (146)	100 consecutive incident cases at the Clinical Centre of Serbia	100 controls among patients treated during the same period for non-malignant diseases of the head/neck, matched on age (± 2 yr), sex and place of residence	Occupational exposure to various chemicals, dust and other agents	Exposure to wood dust[1]	2.3 (1.0–5.7)	[1]Education, BMI, smoking, alcohol, family history of cancers [2]Smoking, dental diseases, HSV infection, smoking, alcohol	
					Occupational exposure to wood dust[2]	4.2 (1.5–11.9)		
Jayaprakash *et al.* (2008) Hospital-based case–control study Buffalo, NY, USA and Germany 1982–98	Sinonasal & nasopharynx & hypopharynx (160, 147, 148)	90 incident cases in men diagnosed at Roswell Park Cancer Institute	1522 controls	Self reported exposures about prior exposure to wood dust at work	Moderate exposure	1.5 (0.9–1.5)	Age, sex, tobacco, education, year of enrollment	
					High exposure	1.35 (0.4–4.6)		
					Occasionally exposed	1.45 (0.85–2.5)		
					Regularly exposed	1.6 (0.75–3.3)		

BMI, body mass index; CI, confidence interval; HLA, human leukocyte antigen; HSV, herpes simplex virus; mo, month or months; yr, year or years

cancer of the hypopharynx among men over the age of 55 years (OR, 2.1; 95%CI: 1.2–3.7), and a decreased risk among men under 55 years (OR, 0.4; 95%CI: 0.2–1.2). Vlajinac *et al.* (2006) observed an increased risk of cancer of the oropharynx (OR, 2.3; 95%CI: 1.0–5.7) associated with wood dust in Serbia and Montenegro.

All five cohort studies published in the period following the previous *IARC Monograph* provided results for cancer of the pharynx, although none provided results for subsites of other than the nasopharynx. The pooled re-analysis of five previously published cohort studies (Demers *et al.*, 1995b) observed slightly fewer cases of cancer of the pharynx than expected (SMR, 0.8; 95%CI: 0.5–1.3). Stellman *et al.* (1998) also found no evidence of an excess risk associated with self-reported wood dust exposure or longest occupation among participants in the Cancer Prevention Study II (RR, 0.9; 95%CI: 0.4–2.0). Innos *et al.* (2000) found an excess risk of cancer of the pharynx among Estonian furniture workers exposed to both medium levels (SIR, 4.0; 95%CI: 0.8–11.8) and high levels of exposure (SIR, 1.5; 95%CI: 0.6–3.3). Dement *et al.* (2003) observed slightly more cases of cancer of the pharynx than expected among members of the US carpenters union (SMR, 1.4; 95%CI: 0.7–2.4). Purdue *et al.* (2006) observed a somewhat reduced risk among Swedish construction workers exposed to wood dust versus those who were not (RR, 0.6; 95%CI: 0.2–1.6, *n* = 4).

2.4 Cancer of the larynx

The previous *IARC Monograph* reviewed ten case–control studies of cancer of the larynx (see Table 27, IARC, 1995). The majority had some indication of an excess risk associated with either wood dust exposure (1/2 studies) or wood-related occupations (7/8 studies), although sometimes based on small numbers. The studies were conducted in the USA (*n* = 7), Europe (*n* = 2), and the People's Republic of China (*n* = 1), and the majority of these studies adjusted for the effects of smoking. No support for this association was found in the cohort studies (see Table 18, IARC, 1995). The five cohort studies that reported results for cancer of the larynx observed fewer cancers than expected.

Seven new case–control studies (Table 2.6) have published results relevant for the evaluation of cancer of the larynx. Pollán & López-Abente (1995) in a Spanish study observed an excess risk among woodworkers (OR, 2.7; 95%CI: 0.9–7.7) that increased with duration of employment. Gustavsson *et al.* (1998) observed a decreased risk for cancer of the larynx associated with wood dust in Sweden (OR, 0.5; 95%CI: 0.3–0.9). Laforest *et al.* (2000) observed no increased risk overall and no evidence of an association with duration or cumulative exposure in a french study (OR, 1.0; 95%CI: 0.6–1.7). Elci *et al.* (2002) also found no association with wood dust in a Turkish study (OR, 1.1; 95%CI: 0.8–1.4). Berrino *et al.* (2003) found an increased risk of cancer of the larynx among men over the age of 55 (OR, 1.7; 95%CI: 1.2–2.6), and a decreased risk among men under 55 (OR, 0.6; 95%CI: 0.3–1.1). Ramroth *et al.* (2008) reported an excess based on a checklist (OR, 2.1; 95%CI: 1.2–3.9), but a weaker association based on a method using a job-specific questionnaire (OR, 1.4; 95%CI: 0.8–2.5). Jayaprakash *et al.* (2008) reported an excess among men based on self-reported exposure (OR, 2.1; 95%CI: 0.9–5.0). Six of the seven studies adjusted for the potential effects of smoking and alcohol consumption, but the last only adjusted for smoking.

All five cohort studies published in the period following the previous *IARC Monograph* provided results for cancer of the larynx. The pooled re-analysis of five previously published cohort studies (Demers *et al.*, 1995b) observed slightly fewer cases of cancer of the larynx than expected (SMR, 0.7; 95%CI: 0.4–1.0), and no association with probability of exposure. Stellman *et al.* (1998) observed a potential excess risk associated with self-reported wood

Table 2.6 Case–control studies of cancer of the larynx and exposure to wood dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Pollán & López-Abente (1995) Hospital-based case–control study Spain January 1982 to August 1985	Larynx (161)	50 male residents of Madrid with histologically confirmed squamous cell carcinomas diagnosed at Ramon y Cajal Hospital	1 hospital control (matched by sex, age, admission date excluding alcohol or tobacco-related conditions) and 1 population control (matched on sex, age, residential census sections at diagnosis)	Extensive job history up to 1 yr before diagnosis; subject was considered exposed at ≥ 1 yr of employment	All woodworkers 1–20 yr > 20 yr	2.7 (0.9–7.7) 1.6 (0.4–5.9) 5.6 (1.2–27.6)	Age, tobacco and alcohol consumption, and other occupational groups	
Gustavsson *et al.* (1998) Community-based case–control study Sweden 1 January 1988 to 31 January 1991	Larynx (161)	401 incident squamous cell carcinomas in all Swedish men aged 40–79 yr living in Stockholm or the southern health care region	Referents randomly selected from the base population and frequency-matched to the cases for region and age group (40–54, 55–64, 65–79 yr)	Exhaustive occupational history taken and exposure assessments were based on a literature survey of exposure data for different occupations	Ever exposed	0.5 (0.3–0.9)	Adjusted for region, age, alcohol consumption and smoking habits	

Table 2.6 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Laforest *et al.* (2000) Hospital-based case–control study France 1 January 1989 to 30 April 1991;	Larynx (161)	296 primary incident squamous cell cancers diagnosed and histologically confirmed in 15 French hospitals; only men were included in the study	Controls were patients with primary cancers of different sites requiring the same medical environment as case cancers, selected by frequency matching on age and recruited between 1987 and 1991 in the same hospitals as the cases or similar hospitals nearby	Detailed lifetime occupational history taken and occupational exposures were assessed through a job–exposure matrix	**Wood dust**		Age, smoking, alcohol, exposure to formaldehyde, and mineral fibres	
					Ever exposed	1.0 (0.6–1.7)		
					Probability of exposure:			
					≤ 70%	0.9 (0.4–2.0)		
					> 70%	1.1 (0.5–2.2)		
					Duration of exposure:			
					< 6 yr	1.4 (0.6–3.2)		
					6–10 yr	0.5 (0.2–1.5)		
					> 10 yr	1.0 (0.5–2.3)		
					Cumulative level:			
					Low (< 10)	1.0 (0.4–2.1)		
					Medium (10–42)	1.2 (0.5–2.8)		
					High (> 42)	0.9 (0.3–2.3)		
Elci *et al.* (2002) Hospital-based case–control study Turkey 1979–84	Larynx (161)	940 cases among men identified from patients admitted to the Oncology Treatment Center of the Social Security Agency Okmeydani Hospital in Instanbul	1519 referent patients with Hodgkin disease, soft tissue sarcoma, non-melanoma skin cancer, testis, bone and male breast cancer as well as a series of non-cancer subjects	Occupational history taken using a questionnaire, occupations coded and exposures assessed using a job–exposure matrix developed for occupational dusts	Wood dust exposure	1.1 (0.8–1.4)	Age, smoking, and alcohol consumption	
					Low intensity	0.8 (0.5–1.4)		
					Med intensity	1.4 (1.0–1.9)		
					High intensity	0.8 (0.4–1.4)		
					Low probability	1.3 (1.0–1.7)		
					Med probability	1.4 (0.7–2.5)		
					High probability	0.4 (0.2–0.9)		

Table 2.6 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)*	Adjustment for potential confounders	Comments
Berrino *et al.* (2003) Population-based case–control study Italy, France, Spain, Switzerland 1979–82	Endolarynx (161)	696 male incident endolarynx cases diagnosed in Calvados, France; Turin & Varese, Italy; Pamplona & Zaragoza, Spain; Geneva, Switzerland	2176 male population controls	Occupational history taken through specialist interview; occupational exposures assessed using a job–exposure matrix	< 55 yr of age:		Age, centre, tobacco, alcohol, diet, socioeconomic status, and exposure to other agents	
					Possible exposure	0.5 (0.2–1.1)		
					Probably exposure	0.6 (0.3–1.1)		
					> 55 yr of age			
					Wood dust exposure	1.7 (1.2–2.6)		
Jayaprakash *et al.* (2008) Hospital-based case–control study Buffalo, NY, USA and Germany 1982–98	Larynx (161)	124 incident male cases diagnosed at Roswell Park Cancer Institute	1522 controls	Self reported exposures about prior exposure to wood dust at work	Moderate exposure	0.8 (0.5–1.3)	Age, sex, tobacco, education, year of enrollment	
					High exposure	2.1 (0.9–4.96)		
					Occasionally exposed	0.8 (0.4–1.4)		
					Regularly exposed	1.5 (0.8–2.8)		
Ramroth *et al.* (2008) Population-based case–control study South-western Germany 1998–2000	Larynx (161)	257 histologically confirmed incident larynx cancer cases in men and women diagnosed in Rhein-Neckar-Odenwald region	769 population controls	Occupational history taken through specialist interview; occupational exposures assessed using exposure substance check-list (SCL), detailed occupational history, supplementary job-specific questionnaires (JSQ)	SCL:		Adjusted for age, sex, tobacco, alcohol, education	
					Wood dust	2.1 (1.2–3.9)		
					Hardwood dust	2.6 (1.3–5.2)		
					Softwood dust	2.2 (1.1–4.2)		
					JSQ:			
					Wood dust	1.4 (0.8–2.5)		
					Hardwood dust	1.2 (0.6–2.5)		
					Softwood dust	1.5 (0.7–2.8)		

CI, confidence interval; RR, relative risk; yr, year or years

dust exposure (RR, 1.6; 95%CI: 0.8–3.4, *n* = 8), but not for wood occupations (RR, 1.2; 95%CI: 0.3–4.9, *n* = 2) among participants in the Cancer Prevention Study II. Innos *et al.* (2000) observed fewer cases of cancer of the larynx than expected (SIR, 0.7; 95%CI: 0.3–1.4) among male Estonian furniture workers. Dement *et al.* (2003) observed slightly more cases of cancer of the larynx than expected among members of the US carpenters union (SMR, 1.2; 95%CI: 0.7–2.0). Purdue *et al.* (2006) observed a somewhat reduced risk among Swedish construction workers exposed to wood dust versus those who were not (RR, 0.8; 95%CI: 0.5–1.5).

Recent registry-based studies also presented results for wood dust and cancer of the larynx. No excess was observed among woodworkers in a large Nordic census-based cancer incidence linkage study (Pukkala *et al.*, 2009). Arias Bahia *et al.* (2005) observed a slight excess of cancer of the larynx in a Brazilian cancer registry and mortality study. Laakkonen *et al.* (2006) found no relationship with wood dust exposure in a Finnish cancer registry study.

2.5 Cancer of the lung

The Working Group for the previous *IARC Monograph* reviewed 24 case–control studies of cancer of the lung (see Table 28, IARC, 1995). Roughly half had some indication of an excess risk associated with either wood dust exposure or wood-related occupations. The studies were conducted in North America (*n* = 11), Europe (*n* = 9), Asia (*n* = 3), and New Zealand (*n* = 1). No support for this association was found in the cohort studies (see Table 18, IARC, 1995). The seven cohort studies that reported results for cancer of the lung observed a similar number of cancers to that expected.

Three new case–control studies (Table 2.7) have published results relevant for the evaluation of cancer of the lung. Wu *et al.* (1995) observed an increased risk of non-small cell lung cancers among African- and Mexican-American men. Matos *et al.* (2000) observed an increased risk for lung cancer among sawmill workers, but not other woodworkers in Argentina. Barcenas *et al.* (2005) observed an excess of lung cancer associated with wood-related occupations or self-reported exposure in an American case–control study. All results were adjusted for smoking.

Four of the five cohort studies published in the period following the previous *IARC Monograph* provided results for cancer of the lung. The pooled re-analysis of five previously published cohort studies (Demers *et al.*, 1995b) observed slightly fewer cases of cancer of the lung than expected (SMR, 0.8; 95%CI: 0.7–0.9). Stellman *et al.* (1998) observed a slight excess risk associated with self-reported wood dust exposure (RR, 1.2; 95%CI: 1.0–1.3), but not for wood occupations (RR, 1.1; 95%CI: 0.9–1.4) among participants in the Cancer Prevention Study II. Innos *et al.* (2000) observed an increased risk among highly exposed female (SIR, 1.6; 95%CI: 0.8–2.9), but not among male Estonian furniture workers (SIR, 1.0; 95%CI: 0.8–1.3). Dement *et al.* (2003) observed an excess among members of the US carpenters union (SMR, 1.5; 95%CI: 1.2–1.7). In a nested case–control study of Polish pulp and paper mill workers, Szadkowska-Stańczyk & Szymczak (2001) observed an excess of lung cancer associated with wood dust exposure (OR, 2.1; 95%CI: 0.9–4.9), but no evidence of an exposure–response relationship.

Recent registry studies also presented results for wood dust and lung cancer. A small excess was observed among women (SIR, 1.2; 95%CI: 1.1–1.4) but not among men (SIR, 0.96; 95%CI: 0.94–0.97) in a large Nordic census-based cancer incidence linkage study (Pukkala *et al.*, 2009). Arias-Bahia *et al.* (2005) observed mixed results in Brazil; a slight excess in the cancer registry study and a decreased risk in the mortality study. Laakkonen *et al.* (2006) found no relationship with wood dust exposure in a Finnish cancer registry study.

Table 2.7 Case–control studies of cancer of the lung and exposure to wood dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Wu *et al.* (1995) Hospital-based case–control study USA	Lung (162)	113 African-American and 67 Mexican-American cases with newly diagnosed lung cancer recruited from the hospitals in Houston and San Antonio, Texas	270 healthy controls without prior histories of cancer from community centres, cancer screening programmes, churches and employee groups frequency-matched on age, ethnicity and sex	Occupational histories collected by interview, self-reported occupational exposure to wood dust	Wood dust exposure	3.5 (1.4–8.6)	Age, sex, mutagen sensitivity, and pack–yr (smoking)	.
					African-American:			
					Non-small cell lung cancer	4.8 (1.2–18.5)		
					Small cell lung cancer	0.7 (0.0–12.4)		
					Mexican-American:			
					Non-small cell lung cancer	3.8 (0.8–17.4)		
					Small cell lung cancer	0.3 (0.0–6.2)		
Matos *et al.* (2000) Hospital-based case–control study Argentina 1994–96	Lung (162)	199 male patients residents in the city or in the province of Buenos Aires and admitted for treatment in any of 4 hospitals of Buenos Aires city	393 controls; 2 male control subjects hospitalized for conditions unrelated to tobacco use during the same period, and residents in the same area, matched by hospital and age (± 5yr)	Occupational history obtained by interview; occupational exposure assessed by job–exposure matrix	Occupation in:		Age group, hospital, pack–yr and industries with $P < 0.05$	
					Sawmills or wood mills	4.8 (1.2–19.0)		
					Furniture	1.0 (0.4–2.2)		
					Woodworkers (carpenters, cabinet-makers, machine operators)	0.7 (0.3–1.5)		

Table 2.7 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	Relative risk (95% CI)*	Adjustment for potential confounders	Comments
Barcenas *et al.* (2005) Hospital-based case–control study USA July 1995 to October 2000	Lung (162)	1368 men and women with incident histologically confirmed lung cancer diagnosed at the University of Texas Cancer Center	1192 cancer-free enrollees of private multispecialty clinics; matched on gender and ethnic groups	Longest held occupation or industry, self-reported wood dust exposure obtained by interview; minimum of 1 yr	Wood related occupation/industry	3.2 (1.5–6.9)	Adjusted for age, gender, ethnicity, smoking status, and place of residence	
					Self-reported wood dust exposure	1.5 (1.2–2.1)		
					Occupation, industry, or self-reported exposure:			
					Lung (adenocarcinoma)	1.5 (1.0–2.1)		
					Non-small cell lung carcinoma (excluding adenocarcinoma)	1.9 (1.3–2.7)		
					Small cell lung carcinoma	1.1 (0.5–2.3)		
Jayaprakash *et al.* (2008) Hospital-based case–control study Buffalo, NY, USA and Germany 1982–98	Lung (162)	809 incident male cases diagnosed at Roswell Park Cancer Institute	1522 controls	Self reported exposures about prior exposure to wood dust at work	Moderate exposure	1.1 (0.9–1.4)	Age, sex, tobacco, education, year of enrollment	
					High exposure	2.15 (1.3–3.6)		
					Occasionally exposed	1.1 (0.8–1.4)		
					Regularly exposed	1.7 (1.2–2.4)		

2.6 Other cancer sites

The results for other cancer sites were reviewed, but were less consistent than for the respiratory tract. The results for case–control studies for wood dust that were published subsequent to the previous *IARC Monograph* are presented in Table 2.8.

2.7 Furniture and cabinet-making industry

The Working Group also addressed the carcinogenic risk associated with the furniture and cabinet-making industry that was evaluated in the previous *IARC Monograph* Volume 25 (IARC, 1981), and reassessed in Supplement 7 (IARC, 1987) when it was classified as *carcinogenic to humans (Group 1)*. Since then, new studies and pooled analyses have strengthened the association between working in this industry and sinonasal and nasopharyngeal cancers, including Fukuda & Shibata (1988), Minder & Vader (1988), Magnani *et al.* (1993), Demers *et al.* (1995a, b) and Bouchardy *et al.* (2002). Such studies are listed among others published since 1980 in Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-09-Table2.9.pdf; Table to 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-09-Table2.10.pdf; Table 2.11 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.11.pdf; Table 2.12 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.12.pdf; Table 2.13 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.13.pdf; Table 2.14 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.14.pdf; Table 2.15 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.15.pdf; and Table 2.16 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-08-Table2.16.pdf.

From reviewing the studies in Tables 2.9 to 2.16 together with the data on exposure to wood dust in Tables 2.1 to 2.8, the Working Group attributed the causal association between working in the furniture and cabinet-making industry and sinonasal and nasopharyngeal cancers to wood dust.

Another possible association observed in the industry included excesses of pleural malignant mesothelioma, which is most likely the result of asbestos exposure. Another possible excess of haematopoietic malignancies may be the result to other exposures such as solvents. Relevant results are presented in Tables 2.11, 2.13, 2.15, but the Working Group considered data for these sites to be inconsistent and inadequate for evaluation.

2.8 Synthesis

There is consistent and strong evidence from both case–control studies and large cohort studies that wood dust causes sinonasal cancer. Most of these studies do not specify the histology of the tumours. Among the case–control that specified histology, very large excess risks were observed for sinonasal adenocarcinoma and wood dust exposure. Case series have found a large proportion of adenocarcinoma cases to be woodworkers.

There is also weaker evidence that wood dust causes cancer of the nasopharynx. The majority of case–control studies observed an increased risk of cancer of the nasopharynx associated with wood dust exposure or with employment in wood-related occupations, although often based on small numbers. This is supported by the pooled re-analysis of cohort studies where a strong association was observed with probability of wood dust exposure. The primary confounder of concern was formaldehyde exposure, but in the pooled cohort study the probability of wood dust exposure, which would likely be inversely

Table 2.8 Case–control studies of other cancers and exposure to wood dust

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)* OR	Adjustment for potential confounders	Comments
Fritschi & Siemiatycki (1996) Population-based case–control study Canada 1979–85	Non-Hodgkin lymphoma (200, 202)	3730 male cases aged 35–70 yr, resident in Montreal, histologically confirmed non-Hodgkin lymphoma, Hodgkin disease, or myeloma	533 colorectal, bladder, prostate, stomach, kidney, melanoma, pancreas and oesophageal cancer controls. 533 population controls selected by electoral lists or random-digit dialling	Occupational history obtained by interview or questionnaire	Wood dust exposure: Non-substantial Substantial	 0.5 (0.3–0.8) 0.8 (0.5–1.3)	Age, proxy status, income (quintiles), ethnicity	Results for wood dust only presented for non-Hodgkin lymphoma
Cocco *et al.* (1998) Census-linked case–control study USA 1984–92	Gastric cardia (151.1)	1056 cases of gastric cardia cancer were identified in men aged 25 yr or more using death certificates from 24 states	5280 control subjects were identified the same way but who died of non-malignant disease; 5:1 match on region, sex, race, and age	Usual occupation obtained from death certificates, exposure was assessed using a job–exposure matrix	Wood dust exposure: Unexposed All exposed Low level exposure Med level exposure High level exposure	 1.0 (reference) 0.8 (0.6–1.1) 0.9 (0.6–1.4) 0.7 (0.5–1.2) 1.0 (0.5–2.2)	Matched on region, sex, race, and age	

Table 2.8 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)* OR	Adjustment for potential confounders	Comments
Cocco *et al.* (1999) Census-linked case–control study USA 1984–96	Stomach (151)	41957 deaths of stomach cancer aged 25+ yr using death certificates from 24 states	83914 controls who died of non-malignant disease; 2:1 match on region, sex, race, and age (± 5 yr)	Usual occupation obtained from death certificates, exposure was assessed using a job–exposure matrix	White men:		Matched on region, sex, race, and age	
					Med probability	0.9 (0.8–1.1)		
					High probability	1.0 (0.9–1.1)		
					Med intensity	1.0 (0.9–1.1)		
					High intensity	0.9 (0.7–1.1)		
					African-American men:			
					Med probability	1.0 (0.7–1.3)		
					High probability	0.9 (0.8–1.2)		
					Med intensity	1.1 (0.9–1.3)		
					High intensity	0.8 (0.6–1.0)		
					White women:			
					Med probability	0.7 (0.4–1.2)		
					High probability	0.8 (0.3–2.2)		
					Med intensity	0.9 (0.7–1.2)		
					High intensity	0.7 (0.3–1.6)		
					African-American women:			
					Medium probability	1.3 (0.5–3.8)		
					Medium intensity	0.9 (0.5–1.6)		
					High intensity	0.4 (0.1–3.4)		

Table 2.8 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)* OR	Adjustment for potential confounders	Comments
Mao *et al.* (2000) Registry-linked case–control study Canada 1994–97	Non-Hodgkin lymphoma (200, 202)	1469 histologically confirmed incident cases (764 men, 705 women) of non-Hodgkin lymphoma diagnosed in 8 Canadian provinces who were 20–74 yr of age	5073 controls frequency matched on age and sex randomly selected from within the same provinces via Provincial Health Insurance Plans, Property Assessment databases, or random-digit dialling	Home or work exposure to 17 chemicals was obtained through questionnaires or interviews	Wood dust exposure:		10-yr age groups, province, BMI (< 20, 20–27, > 27), consumption of milk	
					Men	0.9 (0.8–1.1)		
					Women	1.4 (1.0–2.0)		
					Never exposed	1.0 (reference)		
					1–6 yr exposure	1.2 (0.7–1.9)		
					≥ 7 yr exposure	1.7 (1.1–2.6)		
De Roos *et al.* (2001) Population-based case–control study Canada & USA 1992–94	Neuroblastoma	538 incident cases under 19 yr of age at 139 participating hospitals	504 cases were identified through random-digit dialling individually caliper-matched to cases on date of birth	Telephone interviews with parents for maternal and paternal occupational history. Self-reported exposure assessed by an industrial hygienist (IH)	Wood dust exposure:		Child's age, maternal race, maternal age, and maternal education	
					Paternal occupational exposure			
					Self-reported exposure	1.4 (0.8–2.3)		
					IH-reviewed exposure	1.5 (0.8–2.8)		

Table 2.8 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)* OR	Adjustment for potential confounders	Comments
Briggs *et al.* (2003) Population-based case–control study USA 1984–88	Non-Hodgkin lymphoma (200, 202) Hodgkin disease (201)	1511 non-Hodgkin lymphoma, 343 Hodgkin disease cases diagnosed among African-American and white men born 1929–53, from Atlanta, Detroit, Connecticut, Iowa, Kansas, Miami, San Francisco, Seattle	1910 controls with no history of the selected cancer identified by random-digit dialling and frequency-matched by birth year, and geographic region of cancer registry	Occupational history collected by professional interviewers	Wood dust exposure:		Age and cancer registry.	
					Non-Hodgkin lymphoma:			
					African-American	1.4 (0.7–2.8)		
					White	1.1 (0.9–1.3)		
					Hodgkin disease:			
					African-American	4.6 (1.6–13.3)		
					White	0.9 (0.7–1.3)		
Fritschi *et al.* (2005) Population-based case–control study Australia January 2000–August 2001	Non-Hodgkin lymphoma (200, 202)	Incident cases of non-Hodgkin lymphoma diagnosed in New South Wales or the Australian Capital Territory; aged 20–74 yr	Controls were randomly selected from the New South Wales and Australian Capital Territory Electoral Rolls, frequency matched on age, sex and region of residence	Lifetime occupational history obtained by telephone interview & mailed questionnaire. Exposure assessment done blindly by an occupational hygienist and a job–exposure matrix	Hardwood dust exposure:	1.5 (0.9–2.4)	Adjusted for age, sex, state and ethnic origin	
					Non-substantial	1.7 (1.0–2.9)		
					Substantial	1.2 (0.6–2.7)		
					Softwood dust exposure:	1.6 (1.1–2.6)		
					Non-substantial	1.7 (1.0–2.8)		
					Substantial	1.6 (0.7–3.8)		

Table 2.8 (continued)

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	RR (95%CI)* OR	Adjustment for potential confounders	Comments
Pan *et al.* (2005) Registry-linked case–control study Canada 1994–97	Brain (191)	1009 incident cases of histologically confirmed primary brain cancer from 8 provinces	5039 population control subjects aged 20–76 yr collected in the same study area	Occupational history obtained through questionnaires. Self-reported exposure	Wood dust exposure:		Age, province of residence, education, alcohol intake, total energy intake, smoking pack–yr, and sex	
					Men	1.3 (1.9–1.4)		
					Women	1.1 (0.8–1.7)		
					Both sexes	1.2 (1.0–1.4)		
Fritschi *et al.* (2007) Population-based case–control study Australia January 2001–August 2002	Prostate (185)	606 histologically confirmed cases in Western Australia, aged 40–75 yr. 402 cases of benign prostatic hyperplasia identified from hospital records	471 controls aged 45–75 yr randomly selected from the Western Australia electoral roll August 2001–October 2002; frequency-matched on 5 yr age groups	Occupational history obtained by questionnaires and interviews. Exposure was assessed for each occupation by an occupational hygienist for probability, frequency and total dose.	Wood dust exposure:		Adjusted for age	
					Prostatic cancer–			
					Not exposed	1.0 (reference)		
					Non-substantial	1.1 (0.8–1.4)		
					Substantial	1.2 (0.5–2.6)		
					Benign prostatic hyperplasia–			
					Not exposed	1.0 (reference)		
					Non-substantial	1.1 (0.8–1.4)		
					Substantial	0.8 (0.4–1.4)		

BMI, body mass index; yr, year or years

correlated with formaldehyde exposure, was associated with nasopharyngeal cancer risk, and an excess was observed among both the furniture workers and plywood workers subcohorts.

There was weaker evidence for other sites such as the pharynx, larynx, and lung. Although positive associations were observed in some case–control studies, the pattern was not as consistent and not supported by positive findings in cohort studies.

The great majority of studies did not report on the specific tree species to which workers were exposed or whether exposure was due primarily to hardwoods or softwoods. The few studies that did address tree species were relevant only for the evaluation of sinonasal cancer. There is strong evidence for an association between sinonasal cancer and exposure to hardwood dusts, based on the results of the few studies that specifically assessed exposure to hardwoods and on the results of case series that identified specific tree species. Among the few case–control studies that assessed the relationship with softwoods, there was a consistent excess risk, but the magnitude of the excess was small in comparison to hardwoods, and the association was primarily with squamous cell carcinoma.

3. Cancer in Experimental Animals

Only a limited number of studies in experimental animals have been published on the carcinogenicity of wood dust. Studies described below include those summarized in the previous *IARC Monograph* (IARC, 1995) as well as studies published since.

3.1 Inhalation

3.1.1 Rat

An inhalation study to determine the carcinogenicity of inhaled oak wood dust with and without wood preservatives was conducted in rats. Six groups of 58–61 female F344 rats were exposed to: 1) 18 mg/m^3 of untreated oak wood dust; 2) wood preservatives containing 1 μg/m^3 lindane and 0.2 μg/m^3 pentachlorophenol (PCP); 3) oak wood dust treated with lindane and PCP; 4) 21 μg/m^3 of sodium dichromate; 5) oak wood dust treated with chromate (wood contained the equivalent of 39 μg/m^3 chromate); and, 6) 72 μg/m^3 of *N*-nitrosodimethylamine (positive control). A group of 115 rats were sham-exposed (negative control). Approximately 24 rats/group were exposed for 25 weeks and approximately 36 rats/group were exposed for their lifespan. The particle size was reported as 2–7 μm. The untreated wood dust contained up to 5 μg/m^3 of chromate. No respiratory tract tumours were observed in the negative controls. The positive control group of animals exposed for their lifespan had an incidence of 12/35 nasal cavity tumours. Respiratory tract tumours occurred less frequently in animals exposed for only 25 weeks than in those exposed for their lifespan. The only significant finding in rats exposed for 25 weeks was an increased incidence over controls of benign tumours of organs other than the respiratory tract in the group exposed to chromate aerosol alone. In the rats exposed to untreated oak wood for their lifespan, 2/36 rats developed malignant tumours of the respiratory tract (one in the oral cavity, one bronchial carcinoma, but none in the nasal cavity); there were no benign tumours of the respiratory tract. There was 1/37 animals exposed to wood dust treated with chromate stain, and 1/34 animals exposed to chromate aerosol for their lifespan that had a nasal cavity tumour, but none were found in the

rats exposed to untreated wood dust (Klein *et al.*, 2001).

Sixteen female Sprague Dawley rats were exposed to 25 mg/m^3 of untreated beech wood dust (70%, ≤ 10 µm; 10–20%, ≤ 5 µm) for 6 hours/day, 5 days/week for 104 weeks. There were 16 untreated controls. In the 15 surviving exposed rats and 15 control rats, no respiratory tract tumours were observed. Incidences of non-respiratory tract tumours did not differ between untreated and exposed rats (Holmström *et al.*, 1989).

Fifteen female Wistar rats were exposed to 15.3 mg/m^3 of beech wood dust (mass median aerodynamic diameter [MMAD], 7.2 µm; geometric standard deviation [GSD], 2.2) for 6 hours/day, 5 days/week, for 6 months, and were observed for up to 18 months. No respiratory tract tumours were found in exposed rats or in 15 untreated controls. The incidence of non-respiratory tract tumours did not differ between exposed rats and untreated controls (Tanaka *et al.*, 1991).

3.1.2 Hamster

One group of 12 and one group of 24 male Syrian golden hamsters were exposed to either 15 or 30 mg/m^3 beech wood dust (70%, ≤ 10 µm; 10–20%, ≤ 5 µm) for 6 hours/day, 5 days/week for either 36 or 40 weeks, respectively. One group of 12 and one group of 24 animals served as untreated controls. No respiratory tract tumours were observed in the 12 animals exposed to 15 mg/m^3, but 1/22 animals exposed to 30 mg/m^3 had an unclassifiable infiltrating malignant nasal tumour (not significantly different from controls) (Wilhelmsson *et al.*, 1985a, b). [The Working Group noted that in the above inhalation studies, the size of the dusts was quite large, which might allow some deposition in the upper respiratory tract, but very little deposition in the lower respiratory tract. No measurement of deposition was made, so the actual exposure is unknown.]

3.2 Intraperitoneal injection

3.2.1 Rat

Female Wistar rats received three weekly intraperitoneal injections of beech wood dust [total dose reported as 250 or 300 mg/animal] suspended in saline, and were held for 140 weeks. No mesotheliomas or sarcomas were reported in the 52 rats examined (Pott *et al.*, 1989). [The Working Group noted the limited reporting of the study. No details on the number of starting animals or on particle size were given.]

3.3 Administration with known carcinogens or other modifying factors

3.3.1 Rat

Four groups of 16 female Sprague-Dawley rats were exposed 6 hours/day, 5 days/week for 104 weeks by inhalation to: air (control); 25 mg/m^3 untreated beech wood dust (70%, ≤ 10 µm; 10–20%, ≤ 5 µm); 14.9 mg/m^3 formaldehyde; or wood dust plus formaldehyde. Metaplastic or dysplastic lesions were observed in rats exposed to formaldehyde with or without wood dust, but the incidences between both groups were not statistically different. No such lesions were observed in control rats or in rats exposed to wood dust alone. No respiratory tract tumours were observed in rats exposed to wood dust or to wood dust plus formaldehyde (Holmström *et al.*, 1989).

Two groups of 20 male Wistar rats were exposed by inhalation to air (control); or 15 mg/m^3 of beech wood dust (MMAD, 7.2 µm; GSD, 2.2) for 6 hours/day, 5 days/week for 6 months. Thereafter, five rats per groups were exposed to 10.2 mg/m^3 of sidestream cigarette smoke for 2 hours/day, 5 days/week for 1 month. The experiment was terminated 18 months after the start of the exposures. No tumours of the

respiratory tract were observed (Tanaka *et al.*, 1991).

3.3.2 Hamster

Two groups of 12 male Syrian golden hamsters were exposed by inhalation to air (control) or 15 mg/m^3 beech wood dust (70%, ≤ 10 µm; 10–20%, ≤ 5 µm) for 6 hours/day, 5 days/week for 36 weeks. Another two groups of hamsters were treated similarly but also received weekly subcutaneous injections of 1.5 mg *N*-nitrosodiethylamine (NDEA) for the first 12 consecutive weeks. No nasal tumours were observed in the four groups. Tracheal squamous cell papilloma incidences were: 1/7, controls; 0/8, wood dust; 3/8, NDEA; 4/8, NDEA plus wood dust (Wilhelmsson *et al.*, 1985a, b).

Two groups of 24 male Syrian golden hamsters were exposed by inhalation to air or 30 mg/m^3 beech wood dust (70%, ≤ 10 µm; 10–20%, ≤ 5 µm) for 6 hours/day, 5 days/week for 40 weeks. Another two groups of hamsters were treated similarly but received weekly subcutaneous injections of 3 mg NDEA for the first 12 consecutive weeks. No respiratory tract tumours were found in control animals. The incidence of these tumours did not differ between the groups treated with NDEA or NDEA plus wood dust (Wilhelmsson *et al.*, 1985a, b).

3.4 Exposure to wood dust extracts

In a lifetime experiment, four groups of 70 female NMRI mice weighing 25–30 g [age unspecified] received skin applications of a mutagenic fraction of a methanol extract of beech wood dust in 30 µL acetone twice a week for 3 months. Positive and negative controls were included in the study (Table 3.1). No effect on survival was observed between the treated groups and the negative control groups. A comparison between mice treated with wood dust extract and mice serving as negative controls indicated an overall carcinogenic effect ($P < 0.01$, χ^2 test) (Mohtashamipur *et al.*, 1989). [The Working Group also noted a dose-dependent increase in the incidence of skin squamous cell papillomas and carcinomas combined or papillomas alone.]

Four groups of 50 male and female Kunming mice were intragastrically administered 0, 1, 2 or 4 g/kg body weight of a water extract of birch wood dust, once a week for 5 weeks. Thereafter, mice were given 0.5% butylated hydroxytoluene for 3 weeks in the diet. The experiment was terminated at experimental Week 15. There was a dose-dependent increase ($P < 0.05$) in lung tumour incidence (0/50, 2/49, 4/48, 7/49, respectively), and multiplicity (0, 0.04, 0.15, 0.24 tumour/mouse, respectively). No significant increase was observed in a similar experiment using an organic extract of birch wood dust (He *et al.*, 2002).

3.5 Exposure to wood shavings

Studies directed at testing the potential carcinogenicity of cedar shavings were inadequate in that they did not have control groups (Vlahakis, 1977; Jacobs & Dieter, 1978).

3.6 Synthesis

Several of the studies investigating the carcinogenicity of inhaled wood dust in rats and hamsters used particles with relatively large MMADs, a design that would enhance deposition in the upper respiratory tract, including the nasal cavity. Despite this design, the results of the animal studies do not confirm the nasal carcinogenicity of wood dust observed in humans. No measurement of the actual deposition of wood dust in the respiratory tract was made, and therefore the amount of the exposure is unknown.

In one study in mice, a methanol extract of beech wood dust was tested by skin application. Although a dose-dependent increase in

Table 3.1 Study in mice exposed to mutagenic fractions of methanolic extracts of dust[a]

Tumour	Negative controls			Extract (g)				Benzo[*a*]pyrene (µg)	
	Untreated ($n = 43$)	Shaven ($n = 44$)	Shaven, acetone-treated ($n = 42$)	2.5 ($n = 43$)	5.0 ($n = 50$)	7.5 ($n = 46$)	10.0 ($n = 49$)	5 ($n = 43$)	10 ($n = 42$)
Skin squamous cell carcinomas	–	–	–	1	–	–	1[b]	1	15
Skin squamous cell papillomas	–	–	–	1	1	6	5[b]	2	5
Skin keratoacanthomas	–	–	–	–	–	1	–	–	2
Skin papillary cystadenomas	–	–	–	–	1	–	–	–	–
Sebaceous gland adenomas	–	–	–	–	–	–	–	2	–
Mammary gland adenocarcinomas	–	–	–	–	4	3	2	1	1
Mammary gland adenoacanthomas	–	–	–	–	–	–	1	–	–
Mammary gland mixed tumours	–	–	–	–	–	–	2	–	–
Fibrosarcomas	–	–	–	–	–	1	–	–	–
Haemangiosarcomas	–	–	–	–	1	–	–	–	–
Neurofibrosarcomas	–	–	–	–	1	–	–	–	–
Lymphomas	–	–	–	–	–	–	1	–	–
Anaplastic carcinomas	–	–	–	–	1	–	–	–	–
Precancerous skin lesions	–	1	2	2	4	8	6	13	18

[a] Dust from untreated, semidry beech wood

[b] [$P < 0.01$; Cochran-Armitage test for trend] where comparisons are made for 0 (acetone-treated controls), 2.5, 5.0, 7.5 and 10 g extract groups, including squamous cell carcinomas and papillomas combined, or papillomas alone

Adapted from Mohtashamipur *et al.* (1989), numbers of animals given are effective numbers

the incidence of skin tumours was observed, this result cannot be used in the evaluation of the carcinogenicity in experimental animals of wood dust per se.

4. Other Relevant Data

4.1 Deposition and clearance of particulates in the nasal region

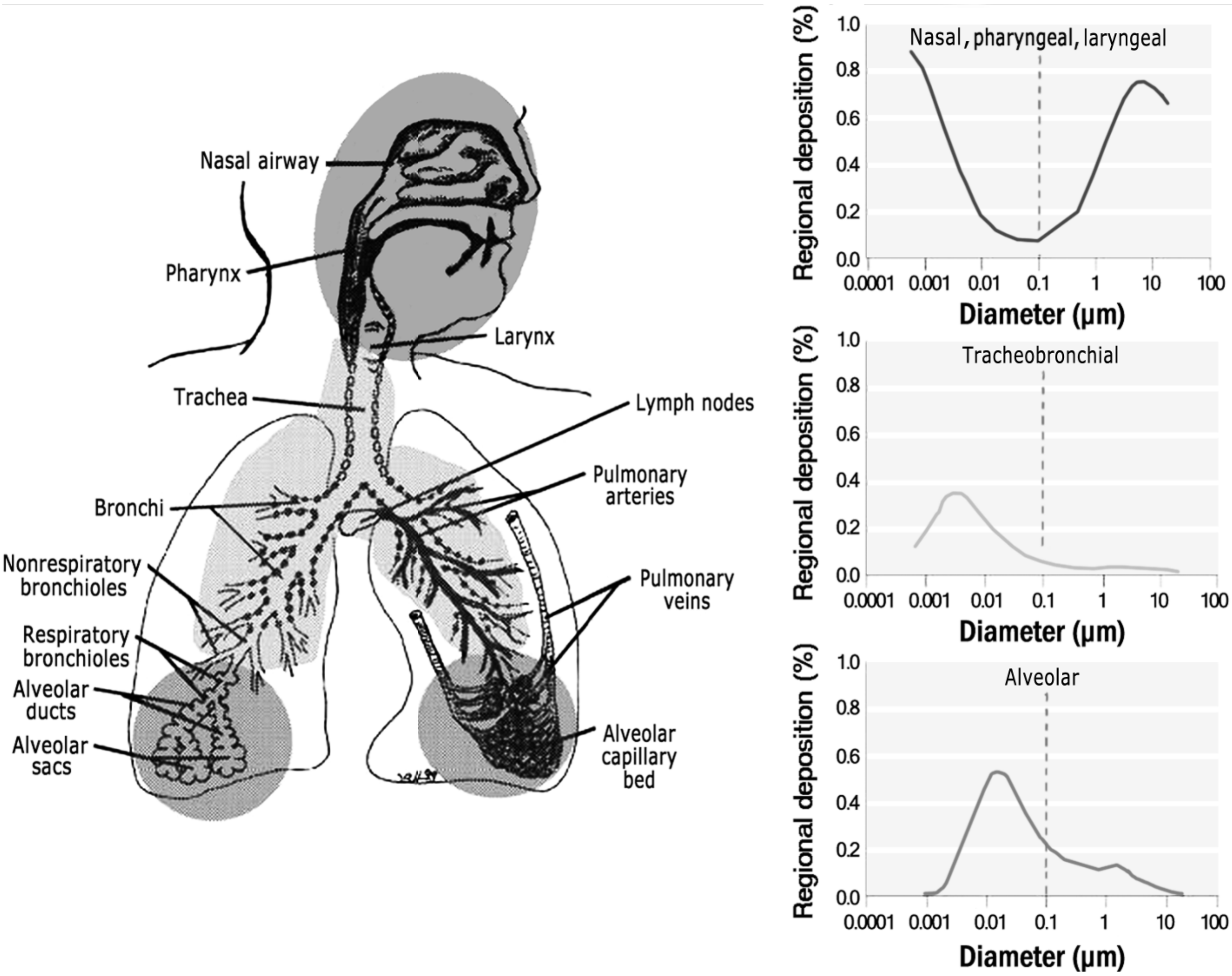
The anatomy and physiology of the upper respiratory tract is complex, and there are significant differences between rodents, non-human primates, and humans (reviewed by Stuart, 1984; Harkema, 1991). Wood dust, leather dust, and metal-containing dusts are complex mixtures that have been associated with the development of sinonasal and nasopharyngeal cancers in humans (IARC, 1995). The nasal region is a primary target of inhaled toxicants. In humans, the particulate fraction of wood and leather dusts is considered to be responsible for carcinogenesis (Fu *et al.*, 1996; Feron *et al.*, 2001). Particulate dosimetry in the upper respiratory tract depends on anatomy, airflow dynamics, and histology. Three-dimensional models have been developed to facilitate interspecies comparisons (Anjilvel & Asgharian, 1995). Humans vary in their breathing patterns at rest and at work; these patterns have an impact on the extent of nasal deposition of particles. In humans, coarse particles (2.5–10 µm) deposit by impaction in the nasal region; very fine particles (less then 0.01 µm in diameter) deposit in the nasopharynx by diffusion (Fig. 4.1; reviewed in Oberdörster *et al.*, 2005). Coarse particles deposited in the nose are rapidly removed by sneezing, sniffing, and mucociliary clearance. However, some areas in the nasopharynx lack cilia, and particles deposited in these regions have longer retention times that can be up to several days (Feron *et al.*, 2001).

4.2 Molecular pathogenesis

The histopathological classification of cancers arising in the sinonasal region (nasal cavity and paranasal sinuses) and in the nasopharynx varies with the anatomical location and associated risk factors (Rosai, 2004). In the sinonasal region, benign tumours or sinonasal papillomas occur; the inverted papilloma subtypes may progress to malignant squamous cell carcinomas in 3–13% of cases (Littman & Vaughan, 2006). The most common malignant tumour in the sinonasal region is squamous cell carcinoma, which is usually associated with cigarette smoking ('t Mannetje *et al.*, 1999), and rarely following exposure to wood dust (see Section 2). Adenocarcinomas are strongly associated with exposure to wood and leather dusts (Fu *et al.*, 1996; d'Errico *et al.*, 2009). Wood dust exposure was associated with a 21-fold [95%CI: 8.0–55.0] increase in the risk of having a sinonasal adenocarcinoma or a squamous cell carcinoma compared to not being exposed (Bornholdt *et al.*, 2008). These occupationally related carcinomas have a unique histological appearance described as intestinal-type sinonasal adenocarcinoma (ITAC). The majority of ITACs are localized in the superior nasal cavity and ethmoid sinus. This cancer develops after a long latent period of 20–30 years of exposure to wood dust, and is locally invasive with rare distant metastases (Llorente *et al.*, 2009). Other malignant sinonasal cancers include cylindrical (transitional) cell carcinoma, small cell neuroendocrine carcinoma, and undifferentiated (anaplastic) carcinoma (Rosai, 2004).

In the nasopharynx, the histopathological classification varies with age and associated risk factors (Yu & Yuan, 2006). Keratinizing squamous cell carcinomas occur at older ages, and the majority of nasopharyngeal carcinomas are non-keratinizing carcinomas, either differentiated or undifferentiated (Rosai, 2004). Non-keratinizing nasopharyngeal carcinomas are more common in high-risk populations in association with

Fig. 4.1 Deposition of inhaled particles in the human respiratory tract during nasal breathing



From Oberdörster *et al.*, (2005). Drawing courtesy of J Harkema. Reproduced with permission from Environmental Health Perspectives.

Epstein-Barr virus infection and other risk factors as discussed in Section 4.4.

4.2.1 Cancer of the nasal cavity and paranasal sinuses

These cancers are extremely rare with only an overall annual incidence of approximately 1/100000 in Europe (Muir *et al.*, 1987). There have been few studies of molecular and genetic alterations associated with the development of sinonasal cancers, and no link to chemical carcinogens has been established (Saber *et al.*, 1998). Inverted papilloma is recognized as a preneoplastic lesion, and mutations in the *p53* tumour-suppressor gene have been associated with progression to squamous cell carcinoma. Epigenetic alterations characterized by promoter hypermethylation have also been identified in sinonasal papilloma (Stephen *et al.*, 2007). In ITACs of patients with known long-term exposure to wood or leather dust, *p14*^{ARF} and *p16*^{INK4a} promoter methylation was detected in 80% and 67% of cases,

respectively (Perrone *et al.*, 2003). In the same study, *p53* mutations were present in 44% (7/16 cases) of the ITACs, and in all but one case the mutations were G:C→A:T transitions in 86% of the cases, and involved the CpG dinucleotides in 50% of the cases. Loss of heterozygosity at chromosomal loci encoding the *p53* (locus 17p13), *p14*^{ARF} and *p16*^{INK4a} (locus 9p21) genes were also reported in 58% and 45% of the cases, respectively (Perrone *et al.*, 2003). *p53* Mutations were previously reported in only 18% (2/11) of sinonasal adenocarcinomas from patients with unknown exposure (Wu *et al.*, 1996). *K-RAS* mutations were also reported in ITACs with a frequency of 13%, whereas the frequency was very low (1%) in squamous cell carcinoma (Saber *et al.*, 1998; Bornholdt *et al.*, 2008). Strikingly, among the five mutations located in codon 12 of the *K-RAS* gene, the G→A transition was the most common, and was present in tumour tissue (adenocarcinoma) from two wood-dust-exposed patients and from one patient with unknown exposure (Bornholdt *et al.*, 2008). [The Working Group noted that a clear link between exposure to wood or leather dust and specific G:C→A:T transitions in ITACs remains to be demonstrated.] Although ITACs resemble colonic adenocarcinomas histologically, alterations in *E-cadherin* and *β-catenin* genes characteristic of the APC pathway and alterations in mismatch-repair genes are rare in sinonasal adenocarcinomas (Perez-Ordonez *et al.*, 2004).

Unique patterns of chromosomal gains and losses have been associated with wood-dust-related ITACs (Korinth *et al.*, 2005; Llorente *et al.*, 2009). Overexpression of c-erbB2 protein was found in one-third of cases (Gallo *et al.*, 1998).

There are no identified precursor lesions leading to the development of ITACs, although hyperplasia, squamous metaplasia, and dysplasia occur frequently in areas adjacent to sinonasal carcinomas (Llorente *et al.*, 2009). A morphological study of nasal biopsies from 139 leather workers employed for a median of 29 years revealed squamous metaplasia in 65% of cases, dysplasia in 41% of cases, and goblet cell hyperplasia in 22% of cases. The presence of goblet cell hyperplasia was associated with longer occupational exposures in leather-tanning activities (Palomba *et al.*, 2008).

4.2.2 Cancer of the nasopharynx

There are few studies of molecular alterations in cancer of the nasopharynx. Many genetic alterations (chromosomal gains and losses) have been described in endemic nasopharyngeal carcinomas, but none of these changes have been specifically linked to wood or leather dust exposure (Hui *et al.*, 1999; Chan *et al.*, 2002).

4.3 Mechanisms of toxicity and carcinogenicity

4.3.1 Tissue injury

Histopathological changes associated with tissue injury and repair (metaplasia, hyperplasia) are extremely common in the upper respiratory tract of experimental animals and humans. In rats, the inhalation of a wide range of volatile and semi-volatile industrial chemicals induces tissue injury, inflammation, and hyperplasia; however, there is no consistent association with subsequent development of nasal cancer. Inflammation, IgE-mediated allergic rhinitis associated with the inhalation of particulate antigens, and inflammatory sinonasal polyps are very common in humans, yet sinonasal cancers are rare as discussed in Section 4.2. Common histopathological changes found in the nasal epithelium include cuboidal and squamous metaplasia and hyperplasia of goblet cells and cylindrical cells. These reactive changes are not considered to be precursors for the development of neoplasia. It is possible that wood dust particles incite tissue injury by direct mechanical damage, although

there are no experimental data to support this mechanism (Feron *et al.*, 2001).

4.3.2 Impaired ciliary clearance and mucostasis

Heavy occupational exposure to wood dust has been reported to impair ciliary clearance, and to contribute to mucostasis (IARC, 1995). Theoretically, the impaired clearance of wood dust particles could lead to prolonged contact with the upper respiratory epithelium (Littman & Vaughan, 2006). Impaired mucociliary clearance may also allow particulate antigens to gain entry to nasal-associated lymphoid tissues, and enhance allergic sensitization (Feron *et al.*, 2001).

4.3.3 Direct genotoxicity

Direct genotoxic effects of wood dust extracts were summarized in IARC (1995). Overall, the mutagenic activity of beech and oak wood extracts was detected in bacterial systems and in rat hepatocytes *in vitro*. Several chemicals were isolated from wood extracts, but only quercetin and Δ^3-carene were shown to be mutagenic (IARC, 1995). Exposure to hexavalent chromium has been associated with the development of sinonasal cancers (Sunderman, 2001).

Dust particles may act as carriers for genotoxic agents. Chromium compounds are often present in oak and beech dusts as they are frequently used in the wood-processing industry, particularly as potassium dichromate in stains as well as fixing agents in wood preservatives. Stained furniture is made largely from oak and beech as they contain enough tannic acid to allow for chemical staining (Klein *et al.*, 2001). Nasal tumours were produced in rats following the inhalation of chromate-stained oak wood dust Klein *et al.* (2001). It was hypothesized that chromate trapped in dust particles is slowly released as hexavalent chromium in the nasal mucosa. Leather workers and tanners are also exposed to hexavalent chromium (Stern *et al.*, 1987). Hexavalent chromium is genotoxic and has been linked with the development of sinonasal cancers in humans (Table 4.1; IARC, 1990).

Table 4.1 Other risk factors for cancers of the nasal cavity and paranasal sinuses[a]

Exposure	Reference
Boot and shoe manufacture and repair	IARC (1987, 2012b)
Formaldehyde	IARC (1995, 2012d)
Hexavalent chromium	IARC (1990, 2012b)
Mineral oils	IARC (1987, 2012d)
Mustard gas	IARC (1987, 2012d)
Selected nickel compounds	IARC (1990, 2012b)
Tobacco smoking	IARC (2002, 2012c)

[a] All classifed as Group 1 carcinogens by IARC

DNA damage (detected by comet assay) in peripheral blood leukocytes was studied in 35 furniture workers and in 41 control office workers. Approximately 20% of woodworkers had elevated levels of DNA damage that did not depend on smoking status compared to 13% of control smokers and 7% of control non-smokers (Palus *et al.*, 1999). [The Working Group noted that the significance of this study is difficult to assess because DNA damage in the sinonasal mucosa was not studied.]

Another group of 60 male furniture workers occupationally exposed for more than 5 years to a mixture of softwood and hardwood dusts (7.4–25.8 mg/m^3) was studied for markers of genotoxicity using peripheral blood lymphocytes and buccal epithelial cells. Controls were 60 healthy male government workers with no history of wood dust exposure. Statistically significant elevations in DNA damage in peripheral blood lymphocytes were detected in workers using the Comet assay. Increased frequencies of micronuclei and chromosomal aberrations were also detected in the peripheral blood lymphocytes of workers. An increased frequency of micronuclei was also detected in buccal epithelial cells obtained from workers. Micronucleus frequency

was increased in both workers and controls who were smokers and consumed alcohol. Serum levels of superoxide dismutase activity and glutathione peroxidase activity, but not catalase activity, were reduced in the workers (Rekhadevi *et al.*, 2009). [The Working Group noted that the authors of this study could not eliminate a potential effect of exposure to chemical adhesives and wood polish in these workers.]

Çelik & Kanik (2006) studied the frequency of micronuclei and other nuclear alterations in exfoliated buccal mucosal cells from 20 workers occupationally exposed to wood dust and 20 healthy controls. Dust levels in the workplace were 4.7–28.9 mg/m^3. In the controls, the micronucleus frequency was 1.5 ± 1.2% compared to 6.6 ± 1.6% in the workers. Evidence of nuclear injury (karyolysis, karyorhexis) and binucleated cells was also increased in the workers. Smokers in both groups showed increased micronucleus frequency and evidence of nuclear injury. [The Working Group noted that the use of buccal epithelial cells as a surrogate for sinonasal mucosa had not been validated.]

The genotoxicity of six wood dusts and dust from MDF coated with oak was compared in the A549 human lung carcinoma cell line (Bornholdt *et al.*, 2007). As determined by a comet assay, beech, birch, teak, pine, and MDF dusts increased DNA strand breaks 1.2–1.6-fold after 3 hours of exposure. [The Working Group noted that the use of a malignant lung carcinoma cell line as a surrogate for sinonasal epithelial cells is questionable, and that no particulate control group was included.]

No data based on genotoxic assays were available to the Working Group for workers exposed to leather dusts.

4.3.4 Indirect genotoxicity

The most likely mechanism proposed for the carcinogenicity of wood dust is a combination of reduced clearance of large particles from the middle turbinate and ethmoid regions of the sinonasal cavity, leading to mechanical irritation, inflammation, and increased cell proliferation (Llorente *et al.*, 2009). In support of the association between chronic inflammation and sinonasal cancer, Holmila *et al.* (2008) analysed COX-2 and p53 protein expression in 23 cases of adenocarcinoma; 17 were exposed to wood dust and 19 were smokers. Elevated COX-2 expression was found in 13 cases including eight cases who were non-smokers; ten of these cases had a history of wood dust exposure. In 50% of the cases with elevated COX-2 expression, there was elevated p53 protein expression in the same histological pattern as COX-2. COX-2 protein expression was confirmed at the mRNA level.

In a murine model of lung inflammation induced by intranasal instillation of birch or oak dusts two times a week for 3 weeks, oak dust induced more inflammation with an influx of neutrophils and lymphocytes compared with birch dust that elicited an influx of eosinophils (Määttä *et al.*, 2006).

These dusts were also tested for induction of pro-inflammatory mediators from murine RAW 264.7 macrophage cell lines. Birch dust increased the release of the pro-inflammatory cytokines IL-6 and TNF-α, and oak dust caused a smaller release of TNF-α. Birch dust also elicited a stronger chemokine response than oak dust (Määttä *et al.*, 2005).

A panel of six wood dusts and MDF dust was assessed for expression of IL-6 and IL-8 pro-inflammatory cytokines using the human A549 lung carcinoma cell line. Based on expression of IL-8 mRNA, teak dust was more potent than MDF, birch, spruce, or pine dust; with beech and oak dust showing the weakest activity in this assay (Bornholdt *et al.*, 2007).

Human alveolar macrophages obtained from healthy volunteers were exposed to endotoxin-free pine dust for 2 hours. This exposure induced a dose-dependent release of the pro-inflammatory mediators, TNF-α and MIP-2, that was

associated with increased production of reactive oxygen species (Long *et al.*, 2004).

No experimental data were available to the Working Group on the release of inflammatory mediators from animals or cell cultures following exposure to leather dusts.

Overall, these experimental studies provide evidence that wood dust from a variety of hardwoods and softwoods can elicit the release of pro-inflammatory mediators after short-term exposures, and suggest a possible association between inflammation and the development of cancer.

In summary, the mechanism responsible for the carcinogenicity of wood or leather dusts is unknown as concluded previously by IARC (1995). In 2000, the Health Council of the Netherlands concluded that wood dust cannot be classified as a non-genotoxic carcinogen or as a direct or indirect genotoxic carcinogen due to insufficient mechanistic data (Feron *et al.*, 2001).

4.4 Other risk factors for sinonasal and nasopharyngeal cancers

The most important exposures associated with the development of sinonasal cancers are occupational exposures in furniture and woodworking industries, leather and shoe manufacturing, and in nickel workers (Table 4.1; IARC, 2012b).

Exposures to other agents classifed by IARC as *carcinogenic to humans (Group 1)* have also been associated with cancers of the nasal cavity and paranasal sinuses (Table 4.1).

Other occupations that have been suggested to be linked with the development of sinonasal cancers include agricultural workers, workers in food manufacturing and preserving, and workers in the textile industry, and in the manufacturing of rubber and plastic products (Leclerc *et al.*, 1997; Luce *et al.*, 2002).

Nasopharyngeal cancers occurring in low-risk populations, including Europe and the US, peak in adolescents and young adults and are associated with Epstein-Barr virus (EBV) infection. The highest risk populations are in the Cantonese region of Southern China and Hong Kong Special Administrative Region, followed by Taiwan, China, the Arctic region, Southeastern Asia, and North Africa. In these high-risk populations, peak incidence is at 50–59 years and the most important risk factors are dietary in association with EBV infection (Yu & Yuan, 2002; IARC, 2012a).

Tobacco smoking is a risk factor for both sinonasal cancer ('t Mannetje *et al.*, 1999; IARC, 2002) and nasopharyngeal cancer, in addition to occupational exposure to formaldehyde or mustard gas (Table 4.2). Squamous cell carcinomas in the nasopharynx have also been linked with exposure to a wood preservative, chlorophenol (Table 4.2; IARC, 1999; Zhu *et al.*, 2002).

It is worth noting that EBV infects almost everyone worldwide but the infection is usually kept dormant by the immune system. Exposure to agents that deregulate the immune system may potentially activate this oncogenic virus (IARC, 2012a).

No published reports were available to the Working Group on genetic susceptibility to development of sinonasal cancers or nasopharyngeal carcinoma associated with exposure to wood or leather dusts.

4.5 Synthesis

Potential mechanisms responsible for the carcinogenicity of wood dust include tissue injury induced by the deposition of wood dust particles in the sinonasal region, impaired ciliary clearance, direct genotoxicity and indirect genotoxicity secondary to chronic inflammation. Wood or leather dusts may also act as carrier for other genotoxic agents (e.g. chromate). There is weak evidence for these mechanisms in cellular assays,

Table 4.2 Other risk factors for nasopharyngeal cancer[a]

Exposure	Reference
Chlorophenol	Zhu *et al.*, (2002), IARC (1999)
Epstein-Barr virus (EBV)	IARC (1997, 2012a)
Ingestion of salted fish and preserved foods during childhood	IARC (2002, 2012c)
Formaldehyde	IARC (1995, 2012d)
Mustard gas	IARC (1987, 2012d)
Tobacco smoking	IARC (2002, 2012c)

[a] All classifed as Group 1 carcinogens except for chlorophenol (2B)

short-term animal assays, or assays for genotoxicity using peripheral blood cells or buccal epithelial cells obtained from workers exposed to wood dust.

Workers exposed to wood or leather dusts have increased frequencies of metaplasia and hyperplasia in nasal epithelial biopsies, although these alterations are not considered to be precursor lesions of neoplasia at this organ site. In one study, leather workers also showed increased evidence of dysplasia in nasal biopsies. No mechanistic data were available to the Working Group for leather dust exposure.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of wood dust. Wood dust causes cancer of the nasal cavity and paranasal sinuses and of the nasopharynx.

There is *inadequate evidence* in experimental animals for the carcinogenicity of wood dust.

Wood dust is *carcinogenic to humans (Group 1).*

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LIST OF ABBREVIATIONS

8-h TWA	Eight-hour TWA
8-OH-dG	8-hydroxydeoxyguanine
AAS	atomic absorption spectrometry
ACGIH	American Conference of Governmental Industrial Hygienists
AG-AAS	Arsine generation atomic absorption spectrometry
AS3MT	arsenic +3 oxidation state methyltransferase
ASA Register	Finnish Register of Workers Exposed to Carcinogens
As–GSH	arsenic–glutathione
BALF	bronchoalveolar lavage fluid
CARET	Beta-Carotene and Retinol Efficacy Trial
CAREX	CARcinogen EXposure
CAS	Chemical Abstracts Service
CBD	chronic beryllium disease
DMAs	dimethylated arsenic species
DMAV	dimethylarsinic acid
DMBA	7,12-dimethylbenz[α]anthracene
DMMTAV	Dimethylthioarsinic acid
DQ12	uncoated quartz
DSMA, or cacodylic acid	disodium methanearsonate
DWA	Daily weighted average
EBV	Epstein-Barr virus
ECVAM	Centre for the Validation of Alternative Methods
EDAX	energy dispersive analysis of X-rays
ET-AAS	electrothermal atomic absorption spectroscopy
F344	Fisher 344
FBs	Ferruginous bodies
Fpg	formamidopyrimidine-DNA-glycosylase
G6PD	glucose 6-phosphate dehydrogenase
GAPDH	glyceraldehyde 3-phosphate dehydrogenase
GC-ECD	gas chromatography-electron capture detection
GF-AAS	graphite furnace atomic absorption spectrometry
GSD	geometric standard deviation
GSH	glutathione
HOBr	hypobromous acid
HOC1	hypochlorous acid
hOGG1	human 8-oxoguanine-DNA-glycosylase
HPV	human papillomavirus

ICP-AES	inductively coupled plasma atomic emission spectroscopy
ICP-MS	inductively coupled plasma mass spectrometry
IMA	International Mineralogical Association
IMIS	Integrated Management Information System
ITAC	intestinal-type sinonasal adenocarcinoma
JEM	job–exposure matrix
LEV	local exhaust ventilation
MBDs	methyl-CpG binding domains
MDF	medium-density fibreboard
MGMT	O6-methylguanine-DNA methyltransferase
MIG/MAG-method	Metal Inert Gas-Metal Active Gas
MLHT	malignant lymphomas of the histiocytic type
MMAD	mass median aerodynamic diameter
MMAs	Monomethylated arsenic species
MMAV	monomethylarsonic acid
MnTBAP	manganese(III)meso-tetrakis(4-benzoic acid)porphyrin
MSHA	Mine Safety and Health Administration
MSMA	monosodium methanearsonate
NDEA	N-nitrosodiethylamine
NHANES III	Third National Health and Nutrition Examination Survey
Ni–Cd	nickel–cadmium
NIOSH	National Institute of Occupational Safety and Health
NOES	National Occupation Exposure Survey
NTP	National Toxicology Program
OEL	occupational exposure limit
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAHs	polyaromatic hydrocarbons
PARP	poly ADP-ribose polymerase
PCP	pentachlorophenol
PD-1	programmed death-1
PMNs	polymorphonuclear leukocytes
PMR	proportionate mortality ratio
RCF-1	refractory ceramic fibres
REL	recommended exposure limit
RLE-6TN	type II lung epithelial cells
RR	relative risk
SHE	Syrian hamster embryo
SiO4	silicate tetrahedron
SIR	standardized incidence ratio
SMR	Standard Mortality Ratio
SV40	simian virus 40
TEM	transmission electron microscopy
TPA	12-O-tetradecanoyl phorbol-13-acetate
TWA	Time-weighted average
UV	ultraviolet
UVR	ultraviolet radiation
XPA	xeroderma pigmentosum group A
XRCC1	X-ray complementing group 1 gene
Zn	zinc

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